FDA Briefing Document

Peripheral and Central Nervous System Drugs Advisory Committee Meeting

November 24, 2015

NDA 206031
Drisapersen

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I. Memorandum to the Committee

MEMORANDUM

DATE: October 28, 2015

FROM: Ronald Farkas, M.D., Ph.D.
Clinical Team Leader
Division of Neurology Products, CDER, FDA

THROUGH: Billy Dunn, M.D.
Director
Division of Neurology Products, CDER, FDA

TO: Members and Invited Guests of the Peripheral and Central Nervous Systems Drugs Advisory Committee (PCNS AC)

SUBJECT: Briefing Memo for New Drug Application (NDA) 206031, for the use of Kyndrisa (drisapersen) for the treatment of Duchenne muscular dystrophy in patients with mutations amenable to exon 51 skipping

The PCNS AC and invited guests will be meeting on November 24, 2015, to discuss the NDA for drisapersen, submitted by BioMarin Pharmaceutical Inc., for the treatment of the subset of Duchenne muscular dystrophy (DMD) patients (≈13%) in whom skipping of exon 51 can restore the reading frame of dystrophin and potentially increase the production of dystrophin, an effect that is theorized to lead to clinical benefit for treated patients.

Disease Background

Key manifestations of DMD include progressive degeneration of skeletal and cardiac muscle resulting in loss of function in childhood and adolescence and premature death from respiratory or cardiac failure in the second to fourth decade. DMD is caused by genetic mutations in the dystrophin gene that result in near absence of the dystrophin protein from muscle. Dystrophin is thought to maintain the structural integrity of the muscle cell membrane by connecting the cytoskeleton to the surrounding extracellular matrix, and to act as a scaffold for several signaling molecules that also contribute to normal muscle physiology. Immunological and inflammatory processes downstream of dystrophin deficiency contribute to

muscle pathology in DMD, and corticosteroid therapy is considered standard of care, delaying loss of ambulation and respiratory decline by several years. No other drugs have been established as effective in DMD and, consequently, a large unmet medical need remains.

Drisapersen Drug Development

Because of the near total lack of dystrophin in DMD, one rational approach to therapy involves trying to restore dystrophin expression. In many patients with DMD, very small amounts of a shorter than normal "truncated" form of dystrophin are produced, due to what might otherwise be considered an error in mRNA splicing: an exon is left out, or "skipped", which, in the setting of specific DMD-causing mutations, can result in restoration of the mRNA reading frame. Unfortunately, the small amount of exon skipping that occurs naturally in DMD patients does not appear to appreciably slow muscle degeneration. It was reasoned, however, that if exon skipping could be augmented by drug therapy, levels of the truncated dystrophin could be increased to a level high enough to confer clinical benefit. Drisapersen was designed to bind to dystrophin mRNA at a specific site to cause the splicing machinery to skip exon 51, thus restoring the dystrophin reading frame in certain amenable patients, and increasing production of the truncated dystrophin. How *much* of the truncated dystrophin would be necessary to confer clinical benefit remains an open question, but a related form of muscular dystrophy, called Becker muscular dystrophy (BMD), provides a natural model of what exon skipping in DMD might achieve. In so-called "exon 51-model" BMD patients, the same truncated form of dystrophin that would be produced by drisapersen in DMD patients occurs naturally. These BMD patients experience a mild, or in some cases asymptomatic, muscle disease. Importantly, however, the truncated dystrophin in these BMD patients is expressed at high levels, roughly 50- to 100% of what would be expected for normal dystrophin.

To support the efficacy of drisapersen, the sponsor undertook two types of studies: biomarker studies to assess whether dystrophin expression was, in fact, increased, and clinical studies, to assess whether the increase in dystrophin had, in fact, resulted in clinical benefit. The design and results of these studies are discussed and reviewed in considerable detail in the draft NDA reviews that we have included in this package. These reviews were conducted by Dr. Veneeta Tandon (efficacy review) and Dr. Evelyn Mentari (safety review), clinical reviewers in the Neurology Division, Dr. Sharon Yan, statistical reviewer in the Office of Biostatistics, Dr. Daniel Krainak, from the Center for Devices and Radiological Health, who acted as a consultant for the Division for the assessment of muscle MRI data, and Drs. Atul Bhattaram (pharmacometrics), Bart Rogers (genomics) and Bei Yu (clinical pharmacology) from the Office of Clinical

Pharmacology. We hope the information in this package will frame the issues we would like you to consider, as well as the briefing materials provided by the sponsor.

A carefully planned and thorough drug development program was undertaken for drisapersen, and we believe that the sponsor and the patients and caregivers who participated in the trials should be recognized for their contributions to the understanding of the drug's safety and efficacy. You will see in the FDA reviews enclosed, however, that it is not clear to the primary review team that substantial evidence of effectiveness has been presented for drisapersen or, consequently, that drisapersen has an acceptable risk-benefit profile. No final decision has been made, however, and the entire review team greatly looks forward to the insights that you can provide at the Advisory Committee meeting.

The concerns of the primary review team are described briefly below.

Biomarkers

It is greatly concerning that a number of biomarker studies suggest that, contrary to initial published reports,[1] drisapersen has little effect on increasing dystrophin levels, the putative mechanism of action. By Western blot, post-treatment dystrophin levels remained very similar to pre-treatment levels, about 1/3rd of 1% of normal. Dystrophin levels with drisapersen treatment thus appear to remain well within the range of the trace levels seen in untreated DMD patients.

We noted that drisapersen *did* decrease creatine kinase (CK) and lactate dehydrogenase (LDH), serum markers of muscle injury in DMD. However, those biomarkers can be affected by many factors that would not predict benefit in DMD, such as decreased physical activity, or that might even indicate harm, such as disease progression.

Some muscle MRI data were included in the NDA, but our internal FDA experts concluded that the MRI studies were not conducted or analyzed with sufficient rigor to be reliable.

Clinical Endpoints

Clinical endpoints were examined in three controlled studies: two Phase 2 studies, and one Phase 3 study. Clinical endpoints were also examined in open-label extension studies that followed controlled studies, including a multi-year extension in 12 patients who participated in one of the early dose-finding studies.

[1] Goemans et al., N Engl J Med 2011;364:1513-1522

The first Phase 2 study, DMD114117 (hereafter Study 117), was a 48-week 3-arm placebo-controlled trial in 53 patients with DMD. Patients were randomized equally to two slightly different dosing regimens, “continuous” or “intermittent”, that provided similar overall drug dose and exposure, or to placebo. Blinding to treatment allocation was, by design, only partial in order to decrease the number of placebo injections. Baseline imbalances were present that appeared to favor the continuous treatment arm. The primary endpoint was the 6 minute walk test (6MWT) at 25 weeks, not the later time point of 48 weeks which is arguably of greater interest for understanding efficacy of chronic therapy. The two doses were each tested at $p < 0.025$ according to the prespecified analysis plan, and the continuous arm of the study was positive, with $p = 0.01$ and a treatment difference of 35 meters vs. placebo. However, the intermittent arm was negative, $p = 0.80$, with a treatment difference of 3.5 meters vs. placebo, and secondary endpoints were uniformly negative. Subsequent analyses at 48 weeks were exploratory due to the earlier negative findings, but if each arm was tested according to the same scheme as used at week 25 (testing at $p < 0.025$) the results were nominally negative, with $p = 0.05$ for the continuous arm and $p = 0.15$ for the intermittent arm. Combining the two drug-treated arms did not appreciably strengthen results, yielding a p-value of 0.12 at week 25 and 0.05 at week 48. Thus, given the inconsistencies in its findings and unimpressive statistical strength, the overall persuasiveness of this study appears to be low.

A second Phase 2 study, DMD114876 (hereafter Study 876), was negative by the usual criteria. The study was a 24 week 3-arm placebo-controlled trial in 51 patients comparing 6 mg/kg or 3 mg/kg of drisapersen to placebo. The p-value for the primary endpoint, 6MWT at 24 weeks for the 6 mg/kg arm, was 0.07, with a treatment difference of 27 meters. The 3 mg/kg arm was numerically *inferior* to placebo. Secondary endpoints were uniformly negative, with some leaning towards inferiority of the drug-treated arms. The p-value of the prespecified per protocol sensitivity analysis was 0.23, due to the removal of one placebo patient who was unblinded after a hospital visit. The independent persuasiveness of this study is thus low.

The considerably larger Phase 3 study (Study 044) was negative, and one of the most plausible post hoc analyses yielded similar negative results. The enrollment criteria for the study allowed entry of patients with more advanced disease compared to the Phase 2 studies, which had limited enrollment to patients that could rise from the floor in ≤7 seconds. Therefore, a post hoc analysis was conducted on the subset of patients in Study 044 who would have met the enrollment criteria for the Phase 2 studies. The result of this analysis, when compared with the primary analysis, showed a *smaller* difference between drug and placebo arms, 5 meters, suggesting that differences in enrollment criteria were not likely to have caused the negative results in Study 044. A number of post hoc subgroup analyses proposed by the sponsor were

found to be highly sensitive to small differences in cutoffs for age and 6MWT and to other specific statistical manipulations, and thus lacked independent credibility.

Patients in a multi-year 12-patient single-arm study of drisapersen had unusually well-preserved function at baseline, which is thought to predict less rapid disease progression, and their disease course was generally similar to historical patients. This study does not appear to provide any support for efficacy.

The primary review team is concerned that treatment allocation may have been substantially unmasked in the clinical trials because of a high incidence of outwardly obvious injection site reactions from drisapersen. The distance walked in 6 minutes is clearly related to effort, and might have been affected by patient and investigator expectation bias if treatment assignments could be deduced.

The current thinking of the primary review team is that evidence supporting the effectiveness of drisapersen is inconsistent.

Safety

Even in the context of an invariably disabling and fatal disease such as DMD, the safety profile of drisapersen is concerning, as described briefly below.

Severe toxicity across many organ systems was encountered in the nonclinical studies, and appeared to predict a number of the adverse events that were subsequently observed in the clinical studies.

Major adverse effects identified in the clinical trials include the following:

- Renal injury
- Thrombocytopenia
- Vascular injury
- Dermal toxicity

Possible Approval Pathways

The decision about approvability is necessarily step-wise, requiring first that the drug be found by FDA to be effective prior to any consideration of benefit-risk.

Efficacy is typically established by positive findings on clinically meaningful endpoints in two adequate and well-controlled trials. Factors that either strengthen or weaken the

persuasiveness of any positive findings should be considered, as should the number and persuasiveness of any negative trials.

A single highly persuasive positive trial combined with independent findings that substantiate efficacy might also support approval, but it is critical that the possibility of an incorrect outcome be considered and that all the available data be examined for their potential to either support or undercut reliance on a single trial.

Under the Accelerated Approval provisions, an effect on a surrogate marker that is determined by FDA to be reasonably likely to predict benefit can support approval. For DMD, there is obvious interest in dystrophin expression as a surrogate marker. Whether an effect on a biomarker such as dystrophin might reasonably predict clinical benefit in DMD is inseparable from such factors as the magnitude and character of the effect on the biomarker, and might also depend on patient factors such as age, disease stage, or secondary inflammation or autoimmunity.

Importantly, the evidentiary standards for effectiveness are not lower for biomarker endpoints used to support Accelerated Approval, nor should Accelerated Approval be used to compensate for weak or inconsistent clinical findings. Negative clinical findings in studies of adequate design and conduct to assess such findings would ordinarily preclude Accelerated Approval on the basis of associated biomarker effects.

Finally, if efficacy is established, the next question is whether a drug's benefits justify its risks. This consideration is made in the broader context of the seriousness of the disease, other treatment options, unmet medical need, risk tolerance of the patient population, etc. Risk-benefit assessment should consider that tolerance for risk may vary among individuals, and may be affected by factors such as disease stage and severity.

II. Drafts Points To Consider

FOOD AND DRUG ADMINISTRATION (FDA)

Center for Drug Evaluation and Research (CDER)

Peripheral and Central Nervous System Drugs Advisory Committee Meeting

DRAFT POINTS TO CONSIDER

November 24, 2015

1. Discuss the findings on biomarkers in the clinical studies and consider their relevance to clinical efficacy, particularly in the context of the existing clinical data.
2. Discuss the findings on clinical efficacy endpoints in the clinical studies, particularly with regard to consistency within and between studies.
3. Discuss the major adverse events identified in the clinical trials, particularly with regard to the acceptability of the risk-benefit profile in the context of this disease.

III. Clinical Efficacy Review

CLINICAL REVIEW (EFFICACY)

Application Type	NDA
Application Number(s)	206,031
Priority or Standard	Priority
Submit Date(s)	4/27/15
Received Date(s)	4/27/15
PDUFA Goal Date	12/27/15
Division/Office	DNP/ODE 1
Reviewer Name(s)	Veneeta Tandon Ashutosh Rao (Dystrophin Bioassays)
Review Completion Date	October 1, 2015
Established Name	Drisapersen
(Proposed) Trade Name	KYNDRISA
Applicant	Biomarin
Formulation(s)	Sterile solution in a single use vial for subcutaneous injection
Dosing Regimen	Loading Dose: 6 mg/kg twice weekly subcutaneous injection for first 3 weeks Maintenance Dose: 6 mg/kg once weekly subcutaneous injection
Proposed Indication(s)	Treatment of Duchenne muscular dystrophy with mutations in the dystrophin gene that amenable to treatment with exon 51 skipping
Intended Population(s)	Exon-51 skip amenable DMD boys
Recommendation on Regulatory Action	

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Glossary

DMD	Duchenne muscular Dystrophy
DAPC	Dystrophin-Associated Glycoprotein Complex
CGH	Comparative Genomic Hybridization
CK	Creatine Kinase
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
GCP	Good Clinical Practices
GSK	Glaxo Smith Kline
H-RMCA	High-Resolution Melting Curve Analysis
ICH	International Conference of Harmonization
ITT	Intent-To-Treat
MLPA	Multiplex Ligation-dependent Probe Amplification
MMRM	Mixed Effect Model Repeated Measure
PP	Per Protocol
SC	Subcutaneous

1 Executive Summary

1.1. Product Introduction

Drug and Indication: KYNDRISA (Drisapersen sodium, also known as GSK2402968 or PRO051) is a new molecular entity that is proposed for the treatment of Duchenne muscular dystrophy with mutations in the dystrophin gene that are amenable to treatment with exon 51 skipping.

Drisapersen is a chemically-modified antisense oligonucleotide (20-mer) with a sequence specific to bind to exon 51 of the human dystrophin pre-mRNA intended to cause the splicing machinery to skip over exon 51 during splicing of pre-mRNA. This restores the reading frame of the resulting mRNA. Restoration of the open reading frame allows the generation of an internally truncated dystrophin that is partially functional. Skipping exon 51 restores the reading frame in patients that carry a deletion of exons 45–50, 47–50, 48–50, 49–50, 50, 52, or 52–63, which, combined, is 13% of all DMD patients.

Pharmacological Class: The proposed Established Pharmacologic Class (EPC) for drisapersen is: *"exon skipping oligonucleotide inducer of dystrophin synthesis"*

Dosage Form: Drisapersen sodium will be available as a 200mg/mL sterile solution in a single use vial for subcutaneous (SC) injection.

Proposed dosage regimen:

Loading Dose: 6 mg/kg twice weekly subcutaneous injection for first 3 weeks
Maintenance Dose: 6 mg/kg once weekly subcutaneous injection

1.2. Conclusions on the Substantial Evidence of Effectiveness

This review concludes that, while there may be some evidence suggestive of efficacy of drisapersen, the evidence is inconsistent and in some cases contradictory, and does not reach the level of substantial evidence.

1.3. Benefit-Risk Assessment

Note: Risk assessments were conducted by Dr. Evelyn Mentari, MD.

Benefit-Risk Summary and Assessment

KINDRISA or Drisapersen is a chemically-modified antisense oligonucleotide (20-mer) with a sequence specific to bind to exon 51 of the human dystrophin pre-mRNA. It is designed to cause the skipping of exon 51 which results in the generation of an internally truncated dystrophin.

Duchenne muscular dystrophy (DMD) is a severe male pediatric neuromuscular disorder that occurs due to the absence of dystrophin protein. DMD is present at birth, but the disorder becomes apparent between ages 3-5 years. The loss of muscle strength in DMD is progressive, leading to loss of ambulation in the teens. Progressive loss of muscle strength leads to decline in respiratory function, cardiac complications and ultimately death typically in the third decade. Exon 51 skip-amenable DMD constitutes 13% of the DMD population, resulting in a prevalence of 2340 boys in the United States. There are no FDA approved treatments of DMD in the Unites States, but glucocorticoids have been shown to prolong function and survival by a few years. Similarly, improvements in supportive care, including physical therapy and assisted ventilation, have led to a steady but slow increase in survival over the past few decades. Chronic glucocorticoid use is associated with Cushingoid syndrome and obesity. There is significant need to treatment options that prolong ambulation and are better tolerated than steroids.

The conclusion of this review is that substantial evidence of clinical efficacy was not established for drisapersen in the treatment of exon 51-skip amenable DMD. There is no independent substantiation of the positive findings from a small Phase 2 study based 6MWD as a clinical endpoint. A larger study intended to provide the most reliable evidence of effectiveness was negative.

Similarly, this review concludes that there is no substantial evidence of an effect on a biomarker that is reasonably likely to predict clinical benefit. Drisapersen had little, if any effect on increasing dystrophin expression, the proposed mechanism of action. An unexpected finding was reduction in serum creatine kinase (CK), potentially a marker of muscle cell integrity, but CK levels are well known to change because of many other non-beneficial effects, such as loss of muscle or decrease in use of muscle, such that the clinical meaningfulness remains inconclusive at this time.

Drisapersen is associated with severe and potentially life-threatening adverse effects. Drisapersen causes immune thrombocytopenia, renal toxicity, and skin injury at injection sites.

- *Thrombocytopenia:* Six drisapersen subjects (2%) had thrombocytopenia $<20 \times 10^9$/L, levels at which patients are at risk potentially fatal complications, including spontaneous intracranial or intrapulmonary hemorrhage. Most of these patients had confirmed anti-platelet antibodies. These cases occurred 14-26 months after the first dose of drisapersen, suggesting that risk increases with duration of exposure. Platelet monitoring every 2 weeks, patient education regarding the signs and symptoms of thrombocytopenia, and facilitating prompt medical assessment and treatment can mitigate this risk. However, the decrease in platelets occurred precipitously and unpredictably so that even with intensive monitoring, the risk remains. Concomitant use of with antiplatelet, thrombolytic, or anticoagulant drugs is not recommended.
- *Renal Injury:* Renal toxicity was reported in 61% of drisapersen 6 mg/kg/week subjects, compared to 34% of placebo subjects. Proteinuria was the most common renal abnormality and occurred in 44% of drisapersen 6 mg/kg/week subjects, compared to 23% of placebo subjects. One patient developed multiple life-threatening thromboemboli in the setting of glomerulonephritis with nephrotic syndrome. Renal laboratory monitoring every 2 weeks and cessation of drisapersen according to recommended laboratory criteria can mitigate this risk but will not eliminate the risk of severe and potentially fatal renal toxicity.
- *Injection Site Reactions:* Injection site reactions occurred in 79% of drisapersen patients and included ulceration, irreversible scarring, and atrophy. The risk for first injection site reaction occurred throughout the first 72 weeks of exposure. 21% of reactions were not resolved by the end of the studies. Reactions known to resolve lasted for a mean of 58 days and up to 1217 days. Injection site reactions occurred despite administration by a medical professional and rotation of injection sites. No

other strategies to mitigate the risk of injection site reactions are known.

The benefit of drisapersen in exon 51 skip amenable patients is inconclusive at this time. Therefore, the benefit-risk assessments were not made.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Duchenne muscular dystrophy (DMD) is a severe pediatric neuromuscular disorder that occurs exclusively in males. DMD is caused by the absence of functional dystrophin protein that protects muscle fibers against contraction damage. Exon 51 skip-amenable DMD, a subgroup of DMD is defined by the presence of exon 51 in the dystrophin gene and the deletion of one or more exons contiguous with exon 51, resulting in an out-of-frame deletion in which the reading frame is restorable by the skipping (removing) of exon-51. • Lack of dystrophin results, through mechanisms not precisely understood, in degeneration of muscle fibers, attracting inflammatory cells and ultimately replacement by fibrotic tissue and adipose tissue. This leads to subsequent loss of muscle strength and function. • Loss of muscle strength is progressive, leaving the patients wheel chair bound by age 10-14. Progressive scoliosis develops that impairs pulmonary and cardiac function. Patients with DMD usually survive until late adolescence but not more than 20 to 25 percent live beyond the twenty-fifth year. • Mutations that are treatable by skipping exon 51 are thought to make up around 13% of the DMD population, resulting in a prevalence of about 2340 boys in the US.	The loss of muscle strength in DMD is progressive leading to loss of ambulation in the teens. Progressive loss of muscle strength leads to decline in respiratory function, cardiac complications and ultimately death typically in the third decade.
Current Treatment Options	• There are no FDA approved treatments of DMD in the Unites States. • The current standard of care is glucocorticoids (prednisone, prednisolone and deflazacort) administered either daily or intermittently with a modest effect. In addition, supportive care such as assisted ventilation and physiotherapy are used to improve quality of life and survival in DMD. • The risks of chronic use of glucocorticoids include increased infections, diabetes, Cushingoid appearance, delayed puberty, behavioral changes, obesity, osteoporosis, and increased frequency of long bone and vertebral fractures.	There is a specific unmet medical need for treatment of exon 51 skip- amenable DMD that will maintain ambulation as long as possible and slow subsequent scoliosis, respiratory and cardiac failure.
Benefit	• KYNDRISA or Drisapersen is a chemically-modified antisense oligonucleotide (20-mer) with a sequence specific to bind to exon 51 of the human dystrophin pre-mRNA. It is designed to cause the skipping of exon 51 which results in the generation of an internally truncated dystrophin. • The development program for drisapersen was exemplary for a severe rare disease, such that beneficial effects on biomarkers and clinical endpoints could have been detected if present. The efficacy of drisapersen was evaluated in one Phase 3 and two Phase 2 randomized placebo controlled trials in ambulant DMD boys ages >5 years in 290 subjects (195 on drisapersen and 95 on placebo) for 24- 48 weeks duration. In addition, two open label extension trials for a total	Studies with drisapersen were adequate and well controlled with an acceptable clinical endpoint, change from baseline 6MWD. No substantial evidence of efficacy was established for drisapersen in the treatment of exon 51-skip amenable ambulant DMD patients There is no independent substantiation of the positive findings from a

<table>
<tr><th>Dimension</th><th>Evidence and Uncertainties</th><th>Conclusions and Reasons</th></tr>
<tr><td></td><td>duration up to 3.5 years intended to provide supportive evidence. Two doses: 3mg/kg/week (n=18) and 6mg/kg/week (n=177) were evaluated in these studies.
• The primary endpoint was change from baseline 6-minute walking distance (6MWD), measured 24 or 48 weeks after treatment. 6MWD is an acceptable, potentially clinically meaningful endpoint. Biomarkers at the mechanistic or molecular level such as dystrophin protein expression, MRI and serum creatine kinase (CK) were measured in some subjects.
• There is no substantial evidence of efficacy for drisapersen. No precise estimate of treatment benefit at 6 mg/kg/week can be established. Note that positive primary endpoint for study DMD114117 was at 24 weeks. At 48 weeks this study showed a decline in change from baseline 6MWD. Study 876 was only placebo-controlled up to 24 weeks. Results below:
<table>
<tr><td rowspan="2">6 mg/kg/week
versus
placebo</td><td colspan="3">6MWD</td></tr>
<tr><td>Study DMD114044
(n=186)</td><td>Study DMD114117
(n=53)</td><td>Study DMD114876
(n=51)</td></tr>
<tr><td>Treatment Difference
(p-value)</td><td>10 m at 48 weeks
(0.42)</td><td>35 m at 24 weeks
(0.01)</td><td>27 m at 24 weeks
(0.07)</td></tr>
</table>
• The weakness of the data include: no independent replication of the results obtained in DMD114117, a decline in change from baseline at Week 49 in the same trial, a different regimen of 6mg/kg dose with identical drug exposure not statistically significant with a p-value of 0.80, a p-value of 0.07 from DMD114876 increased to a p-value of 0.21 after removing a single placebo subject that was unblinded during the study.
• There were multiple secondary endpoints expected to be correlated with the primary endpoint but these generally were not statistically significant in any of the studies, and increase doubt about the robustness of the result on 6MWT.
• Drisapersen was designed to increase dystrophin expression, but any increase in dystrophin protein expression was equivocal. Any effect on dystrophin appears so small as to be unlikely to have resulted in clinical benefit.
• There was a 30-40% reduction in CK in the placebo controlled studies based on percent change from baseline CK, but the clinical meaningfulness of this is uncertain due to the presence of cofounders that reduce CK.
• A small amount of muscle MRI data was collected, but the data was not reliably collected and the results were equivocal.
• The open label studies did not provide evidence of slower progression based on known natural history of DMD patients.</td><td>small Phase 2 study. A larger study intended to provide substantiation of effectiveness was negative. One can argue the reduction in serum creatine kinase to be plausibly treatment related, but it remains inconclusive at this time.</td></tr>
</table>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk	• The safety database for drisapersen includes all patients from the 3 Phase 2 and Phase 3 placebo controlled trials and from the 3 open label studies. Drug exposure is adequate and reflects the intended population for use. • The most common AEs were: Injection site erythema (52%), Proteinuria (44%); injection site discoloration (36%). • Six drisapersen subjects (2%) had thrombocytopenia <20 x 10^9/L, levels at which patients are at risk potentially fatal complications, including spontaneous intracranial or intrapulmonary hemorrhage. These cases occurred 14-26 months after the first dose of drisapersen. Despite routine monitoring of platelets every 2 weeks, thrombocytopenia occurred precipitously in some cases. • Renal abnormalities occurred in 61% of patients taking drisapersen, and the risk for a renal adverse event existed throughout 72 weeks of exposure. Proteinuria occurred in 44% of drisapersen 6 mg/kg/week patients, compared to 23% of placebo patients. Proteinuria was generally reversible on discontinuation, although one patient had life-threatening glomerulonephritis with nephrotic syndrome and multiple thromboemboli. • Injection site reactions, including discoloration, induration, pain, pruritus, bruising, atrophy, hematoma, and swelling, occurred in 79% of drisapersen patients. In 5% of all drisapersen patients, injection site reactions led to ulceration, fibrosis/sclerosis, or calcification. The risk for first injection site reaction occurred throughout the first 72 weeks of exposure. 21% of reactions were not resolved by the end of the studies. Reactions known to resolve lasted for a mean of 58 days and up to 1217 days. • Concomitant use with antiplatelet, thrombolytic, or anticoagulant drugs is not recommended. Patients taking these drugs were excluded from clinical studies. • Safety in the postmarketing setting: Laboratory values as markers of renal and thrombocytopenia adverse events were closely monitored during the clinical studies, and close monitoring will be necessary in the postmarket setting if the drug is approved. • Other uncertainties: The clinical effects of anti-drisapersen antibodies. The clinical effect of pro-inflammatory activity.	Major safety issues of thrombocytopenia, renal adverse events, and injection site reactions occur at the proposed dose of drisapersen. The safety issues can have life-threatening outcomes; the adverse reactions can be mitigated but not completely prevented with monitoring. The magnitude of the potential for serious harm after approval is unknown. Adherence to monitoring of platelets and renal laboratory parameters every two weeks is necessary, and failure to adequately monitor, recognize signs and symptoms, and provide prompt medical treatment in the postmarketing setting would increase the risk of adverse and potentially life-threatening outcomes. Injection site reactions occurred despite administration by a medical professional and rotation of injection sites. No other strategies to mitigate the risk of injection site reactions are known. Based on nonclinical findings and because of limitations due to the small number of patients exposed and duration of exposure in the clinical trials it is likely that adverse reactions not identified to date will occur in the postmarketing setting.
Risk Management	If drisapersen is approved, the following risk management approaches are recommended: • A patient registry as a post-marketing requirement will help to evaluate the main safety risks of drisapersen in the postmarketing setting. • Strong product labeling including a boxed warning and a Medication Guide with recommendations for monitoring of laboratory parameters and for rotation of injection	A patient registry as a post-marketing requirement will help to evaluate the main safety risks of drisapersen in the post-marketing setting. A boxed warning should be included in

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	sites is necessary to mitigate the risks of renal and thrombocytopenia adverse events and of injection site reactions. However, even with adequate monitoring, some patients will likely experience serious adverse events.	labeling to describe the risks of renal adverse events and thrombocytopenia and to provide recommendations for monitoring and to warning of the risk for injection site reactions and provide recommendations for rotation of injection sites. A medication guide should be required to describe these risks and symptoms of concern, and to highlight the need for prompt medical attention.

2 Therapeutic Context

Analysis of Condition

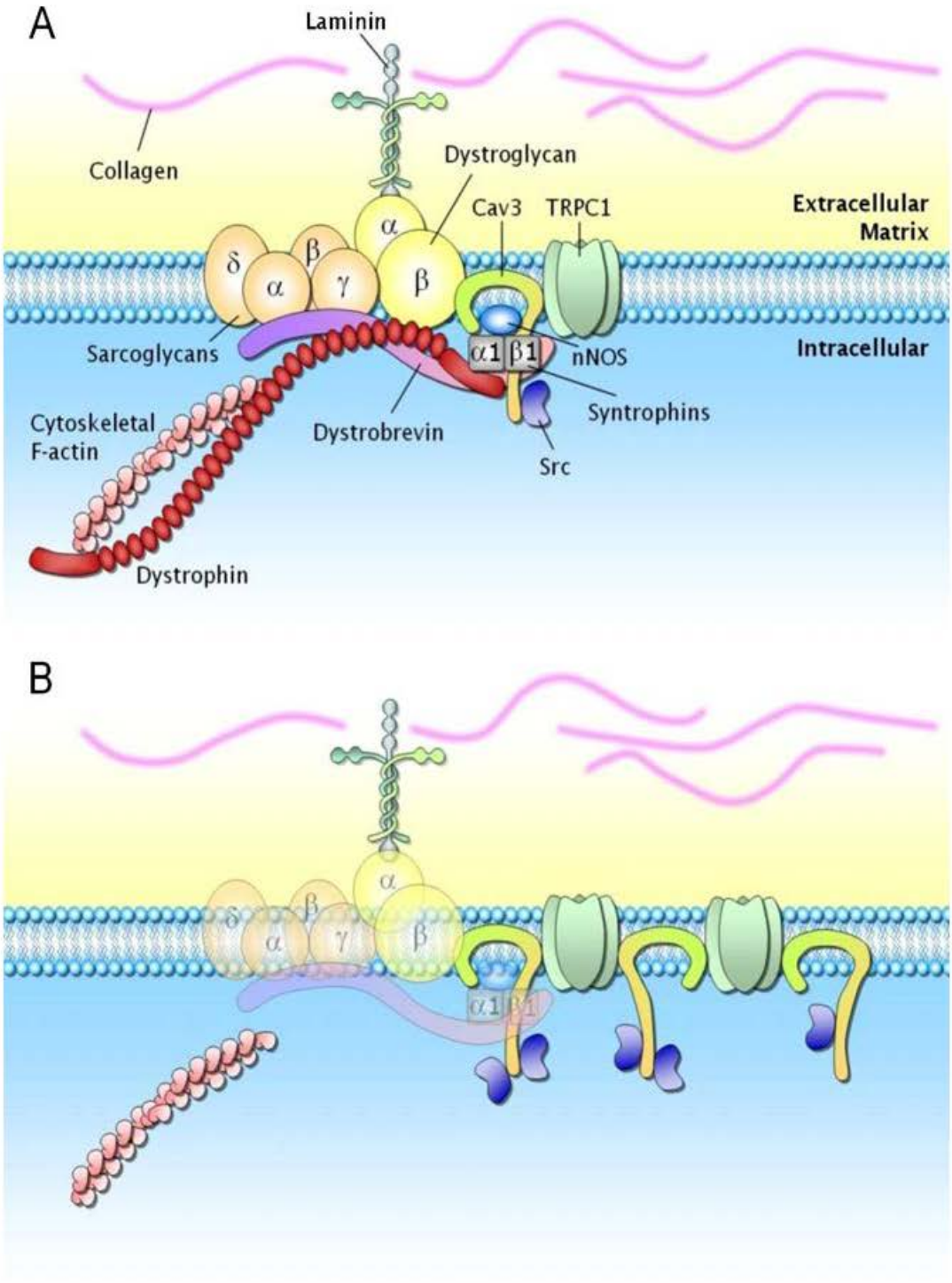
Duchenne muscular dystrophy (DMD) is the most frequent of the early onset muscular dystrophies that occur almost exclusively in males (X-linked recessive disorder). A small percentage of female carriers may exhibit a range of muscle symptoms from the full Duchenne phenotype to milder skeletal muscle weakness. Exon 51 skip-amenable DMD, a subgroup of DMD is defined by the presence of dystrophin exon 51 and the deletion of one or more exons contiguous with exon 51, resulting in an out-of-frame deletion in which the reading frame is restorable by the skipping (removing) of exon-51.

Etiology: DMD is caused by the absence of functional dystrophin protein due to mutations in the DMD gene. Mutations that disrupt the translational reading frame of the dystrophin transcript, lead to a prematurely aborted dystrophin synthesis. The resulting dystrophin deficiency at the muscle fiber membranes leads to progressive fiber degeneration. The most common mutation is exon deletions (~60%) (Aartsma-Rus 2002). Dystrophin provides structural stability to the dystrogylcan complex on the muscle cell membranes, protecting muscle fibers against contraction induced damage. In addition, the association of dystrophin with catalyzing enzymes (nitric oxide synthases) completes the link between the extracellular matrix and intracellular signal transduction enzymes (Brenman 1995, Allen 2011) (Figure 1). Dystrophin is expressed in the skeletal, cardiac, and smooth muscle, as well as in the brain.

Lack of dystrophin results, through mechanisms not precisely understood, in degeneration of muscle fibers, attracting inflammatory cells and ultimately replacement by fibrotic tissue and adipose tissue. Dystrophin deficiency results in loss of neuronal nitric oxide synthase, which normally is localized to the sarcolemma as part of the dystrophin–glycoprotein complex. The absence of functional dystrophin in DMD results in deterioration of the skeletal musculature with subsequent loss of strength and function (Bushby 2010).

Clinical Features: DMD is present at birth, but the disorder usually becomes apparent between ages 3 and 5 years. There is a proximal-to-distal progression of muscle weakness. The boys fall frequently. Running, jumping, and hopping are invariably abnormal. By age 5 years, muscle weakness is obvious by muscle testing. On getting up from the floor, the patient uses his hands to climb up himself. Contractures of the heel cords and iliotibial bands become apparent by age 6 years, when toe walking is associated with a lordotic posture. Loss of muscle strength is progressive, with predilection for proximal limb muscles and the neck flexors; leg involvement is more severe than arm involvement. Between ages 8 and 10 years, walking may require the use of braces. By age 10-14, patients become wheel chair bound. Contractures become fixed, and a progressive scoliosis often develops. The chest deformity with scoliosis impairs pulmonary function, which is already diminished by muscle weakness. By age 16–18 years, patients are predisposed to serious, sometimes fatal pulmonary infections. In the last years of life the patient becomes bedfast. In general, there is a wide range of functional ability at a given age.

Figure 1 (A) Dystrophin-Associated Glycoprotein Complex (DAPC); (B) Protein changes in dystrophic muscle



Source: Allen 2011

The use of glucocorticoids and the management of spine deformity, pulmonary and cardiac dysfunctions have altered the timing of some of the clinical milestones of the disease.

Life Span: Patients with DMD usually survive until late adolescence but not more than 20 to 25 percent live beyond the twenty-fifth year. Respiratory, orthopedic and cardiac complications emerge, and without intervention the mean age at death is around 19 years (Bushby 2010). Following the introduction in the 1990s of assisted ventilation in the later stages of the disease, the mean age of survival (for those ventilated patients who do not develop early and severe cardiomyopathy) shifted to 24 years, with some surviving to the early thirties (Rall 2012, Eagle 2002).

Incidence: The incidence of DMD is 13 to 35 per 100,000 yearly or about 1 in 3,500 live male births globally. The estimated prevalence in the US is 18,000, with an additional 15,000 cases in EU (McNeil 2009). Mutations that are correctable by skipping exon 51 are thought to make up around 13% of the DMD population, resulting in a prevalence of 2340 boys in the US and 1950 boys in the EU.

Diagnostic Criteria: All boys with a clinical suspicion of a DMD diagnosis are subjected to molecular analysis of their dystrophin gene. Molecular methods that assess DNA copy number are used as the initial step in the diagnosis of DMD. If no deletions are identified, then DNA sequencing is performed to identify point mutations or small insertions or deletions. Three commonly used tests to determine a patient's mutation in the dystrophin gene include Multiplex Ligation-dependent Probe Amplification (MLPA), High-density Array Comparative Genomic Hybridization, and Single-Condition Amplification Internal Primer Sequencing.
Serum CK levels are invariably elevated to between 20 and 100 times normal. The levels are abnormal at birth but decline late in the disease because of inactivity and loss of muscle mass. EMG demonstrates features typical of myopathy.

2.2. Analysis of Current Treatment Options

There are no FDA approved treatments of DMD in the US that will prevent or slow muscle weakness in DMD. The current goals of treatment are to maintain function for as long as possible and to manage associated complications, such as joint contractures, scoliosis, cardiomyopathy, respiratory insufficiency, and weight gain.

The current standard of care is glucocorticoids (prednisone, prednisolone and deflazacort) administered either daily or intermittently. There is no consensus of the dosing regimen of these glucocorticoids globally. Most frequent regimens include 0.75 mg/kg/day prednisone, 10 days on/10 days off, 0.9 mg/kg/day deflazacort, and 5 mg/kg/day on weekends (Griggs 2013). The recent natural history studies have shown that the use of glucocorticoids have changed the natural progression of the disease. Randomized controlled trials published in literature have shown that glucocorticoids improved muscle strength and function for six months to two years. Data from non-randomized studies suggests functional benefit over a five year period in many treated patients, but the overall long-term benefit remains unclear (Cochrane Review). The risks of chronic use of glucocorticoids include increased infections, diabetes, Cushingoid appearance, delayed puberty, behavioral changes, obesity, osteoporosis, and increased frequency of long bone and vertebral fractures.

In addition, supportive care such as assisted ventilation and physiotherapy are used to improve quality of life in DMD.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Drisapersen is a new molecular entity and is not currently marketed in the US.

3.2. Summary of Presubmission/Submission Regulatory Activity

Drisapersen was initially licensed by Prosensa, who conducted the Phase 1 studies and an open label extension of the Phase 1 study. It was licensed by GSK in 2010. GSK suspended dosing in all studies following the results of the Phase 3 study DMD114044. Subsequently rights were regained by Prosensa and more recently in January 2015 Biomarin acquired Prosensa.

A brief chronology of the regulatory activity with GSK, Prosensa and Biomarin and FDA on the development of drisapersen primarily as it relates to the assessment of efficacy mainly and additional important milestones is tabulated below. The regulatory interactions regarding different review disciplines will be addressed in the respective reviews (i.e. chemistry, nonclinical and safety).

Date	Summary of Regulatory Activity
8 July 2009	Pre-IND meeting with Prosensa; concerns raised by FDA at the meeting were: • 6 mg dose selection based on the 5 week CLIN-02 study may not be adequate, not clear if 6 mg was the MTD. • 6MWD as a primary endpoint acceptable provided 'large enough benefit', supportive data from secondary endpoints will be important due to concerns of unblinding due to injection-site reactions. • Need steps to minimize risk and potential effects of unblinding. • Difficulty in supporting the safety of a 12-month pivotal based on limited human data. • Implementation of adequate safety monitoring for platelet, liver and renal effects. • Need to take confounding factors such as non-invasive ventilation, use of glucocorticoids, scoliosis and surgery into account for randomization scheme or analytical plan.
25 August 2009	FDA grants Orphan Drug Designation to Prosensa
8 April 2010	GSK submitted IND105284 to the FDA Division of Neurology Products, including protocol DMD114118 (single dose PK, safety/tolerability study)

7 June 2010	FDA puts IND105284 on Partial Clinical Hold (only single dose in study DMD114118 is allowed to proceed, not the open label extension) for following reasons: • AEs in previous human studies not described in sufficient detail based on ICH3 Guidelines • Inadequate monitoring of hematological, hepatic and renal effects • Inadequate information on open label extension part DMD 114348
1 November 2010	GSK provides response to the Partial Clinical Hold, including submission of dose ranging protocol DMD114876
6 December 2010	FDA grants Fast-Track Designation to drisapersen
18 January 2011	FDA continues Partial Clinical Hold as 39 week study in monkey induced vascular injury at all doses. There was thrombus formation at two high doses.
4 May 2011	FDA removes Partial Clinical Hold, multiple dosing in protocol DMD114876 is allowed to proceed; Division proposes exclusion, monitoring and discontinuation rules.
4 January 2012	FDA requests additional safety information regarding recent adverse events of proteinuria
2 March 2012	GSK submits new protocol with new safety criteria to monitor and manage future events of proteinuria that is agreed with FDA
7 March 2013	Teleconference to discuss safety monitoring and managing regarding an adverse event of venous sinus thrombosis
23 May 2013	EOP2 Meeting with GSK. Issues discussed at this meeting were: • Pathway of approval: FDA did not consider "accelerated approval" based on Phase II studies as the regulatory course for drisapersen because 6MWD is a clinically meaningful endpoint. Top lines results of the Phase III study were to be available 4 months after the EOP2 meeting. FDA recommended that NDA based on Phase II (DMD114117, DMD114876) and Phase III (DMD 114044) along with results from DMD114763 appear most appropriate. FDA was open to considering dystrophin expression as supportive along with 6MWD to support filing of NDA, but was unclear with the current data were adequate. • FDA recommended immunogenicity be adequately addressed for both drug product and dystrophin. GSK indicated that there was no risk of immunogenicity with AON product. The FDA recommended that GSK provide supportive data explaining why AONs do not need immunogenicity assessments. • FDA agreed to the possibility of a rolling review of the NDA.
26 June 2013	FDA grants Breakthrough Therapy designation for drisapersen based on the results of Study DMD114117 and the 141 week open label study DMD 114673.
02 June 2014	Prosensa receives FDA communication on regulatory path forward. • FDA expresses reservations about the persuasiveness of the available data, but open to filing an NDA for drisapersen for consideration under an accelerated approval pathway. • FDA advised that the 6MWD could be interpreted as an intermediate clinical endpoint, supplemented by relevant evidence supporting reasonably likelihood

	of predicting longer term benefits. • FDA advised on types of confirmatory studies.
22 October 2014	Prosensa participates in Type C meeting with FDA to discuss confirmatory trials. FDA recommends a 2-3 year long confirmatory study. Prosensa agreed with conducting a longer 2-3 years study with an interim analysis. No agreement has been reached on the design of the confirmatory study in subsequent interactions with Biomarin.
12 January 2015	Pre-NDA meeting with FDA, Prosensa and Biomarin. The following agreements were reached: • Antibody data from supportive studies to be submitted at the 120-safety update • DMD natural history data collected by CINRG to be included at the time of NDA submission. • FDA disagreed with Biomarin's proposal to submit only Dr Goeman's natural history data for comparisons based on age and 6MWD and CINRG data for interpretation of pulmonary function in Study DMD114673. FDA explained that totality of available natural history data, including Dr Goeman's data and the CINRG data and any other natural history data would need to be provided at the time of NDA submission to enable appropriate review. FDA did not agree that matching would be adequate if based on 6MWD and age alone. Additional data, such as ability to jump and hop and detailed history corticosteroid use would be necessary. The sponsor agreed to include all natural history data available to the sponsor at the time of NDA submission. **Note: CINRG natural history data was not submitted in the application, and could not be obtained by FDA from CINRG. Matching was only done based on age and 6MWD. Additional data, such as ability to hop, jump etc. from Goeman's natural history data were not provided in the application.**
9 April 2015	FDA did not agree that a 24 week randomized double blind placebo controlled confirmatory study with drisapersen followed by a 72 week open label extension study would provide convincing evidence of benefit given the bias associated with potentially unblinding adverse effects on an effort dependent endpoint.

3.3. Foreign Regulatory Actions and Marketing History

Drisapersen has not been submitted for approval in any other country.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The review was pending at the time completion of this review.

4.2. Product Quality

The applicant proposes the to-be marketed Drisapersen sodium injection for subcutaneous use be available as 160mg/0.8 mg ad 100 mg/0.5 mg single use vials. The CMC reviewer recommends eliminating the counterion name from the product and expressing the product strength as drisapersen and not as drisapersen sodium This will change the dosage strength to 150.4 mg (equivalent to 160 mg drisapersen sodium)/0.8 mL and 94 mg (equivalent to 100 mg drisapersen sodium)/0.5 mL in single-use vials.

4.3. Clinical Microbiology

Not applicable

4.4. Nonclinical Pharmacology/Toxicology

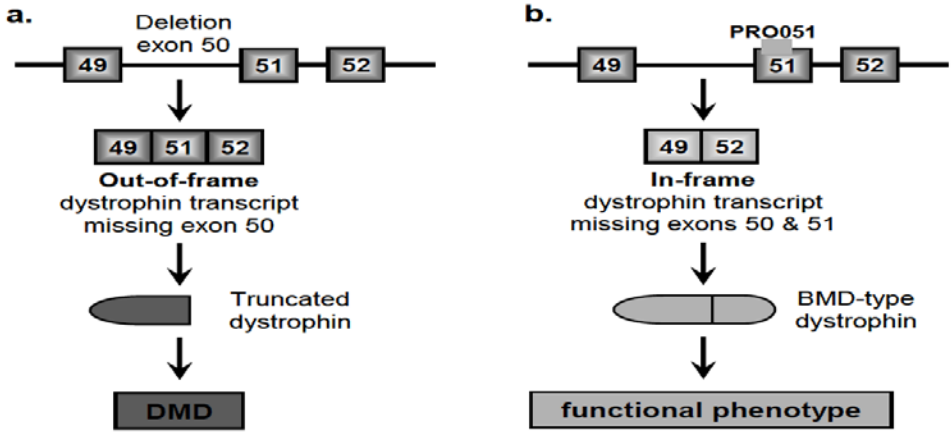
The review was pending at the time of completion of this review.

4.5. Clinical Pharmacology

4.5.1. Mechanism of Action

Drisapersen is a chemically modified oligonucleotide (fully 2'*O*-methyl substituted RNA backbone with phosphorothioate linkages) to promote RNA binding and prevent mRNA breakdown after binding. According the Applicant, drisapersen has high sequence specificity to exon 51. The Applicant's proposed mechanism of action involves disruption of secondary structure and/or interference with the binding of splicing regulatory proteins, resulting in skipping of exon 51 during post-transcriptional splicing and a mature mRNA transcript that is internally shorter but capable of dystrophin production in DMD. The truncated dystrophin lacks amino acids in the central rod domain, but retains the N- and C-terminal domains necessary for its structural and signaling roles. Drisapersen-induced exon skipping has a mutation-dependent corrective approach. Skipping of one specific exon applies to a series of different mutations. Skipping exon 51 with drisapersen would restore the reading frame in patients that carry a deletion of exons 45–50, 47–50, 48–50, 49–50, 50, 52, or 52-63, which comprise a total of 13% of all DMD patients. The exon skipping mechanism by drisapersen is shown schematically in Figure 2 in a patient that has exon 50 deletion.

Figure 2: Schematic representation of exon skipping mechanism



4.5.2. **Pharmacodynamics**

The results of dystrophin analysis are discussed section 6 of the review for each individual study.

4.5.3. **Pharmacokinetics**

- In Plasma:
  - Maximum plasma levels are generally reached between 2 to 4 hours after SC administration, after which the plasma levels decline during a rapid initial tissue (re)distribution phase, followed by a slower elimination phase.
  - After 24 weeks of dosing, the trough plasma concentrations at Week 36 (12 weeks after stopping treatment) were approximately half of the trough concentration at Week 23, indicating drisapersen has a long terminal half-life.
  - In DMD subjects the major drug-related component in plasma after repeated SC administrations was unchanged drisapersen.
  - No studies have been performed specifically to evaluate excretion in humans, but mice studies suggest it is mainly through the urinary route.
- In Skeletal Muscle:
  - Drisapersen concentrations in the muscles reach maximum levels after 39 weeks of dosing.
  - Drisapersen is also eliminated slowly from the muscle tissues with concentrations declining 40% after 12 weeks of stopping treatment.

4.6. **Devices and Companion Diagnostic Issues**

Development of a companion diagnostic was not required because DMD mutation analysis is incorporated in DMD diagnosis, and thus occurs prior to, and separate from, consideration of a therapeutic.

4.7. **Consumer Study Reviews**

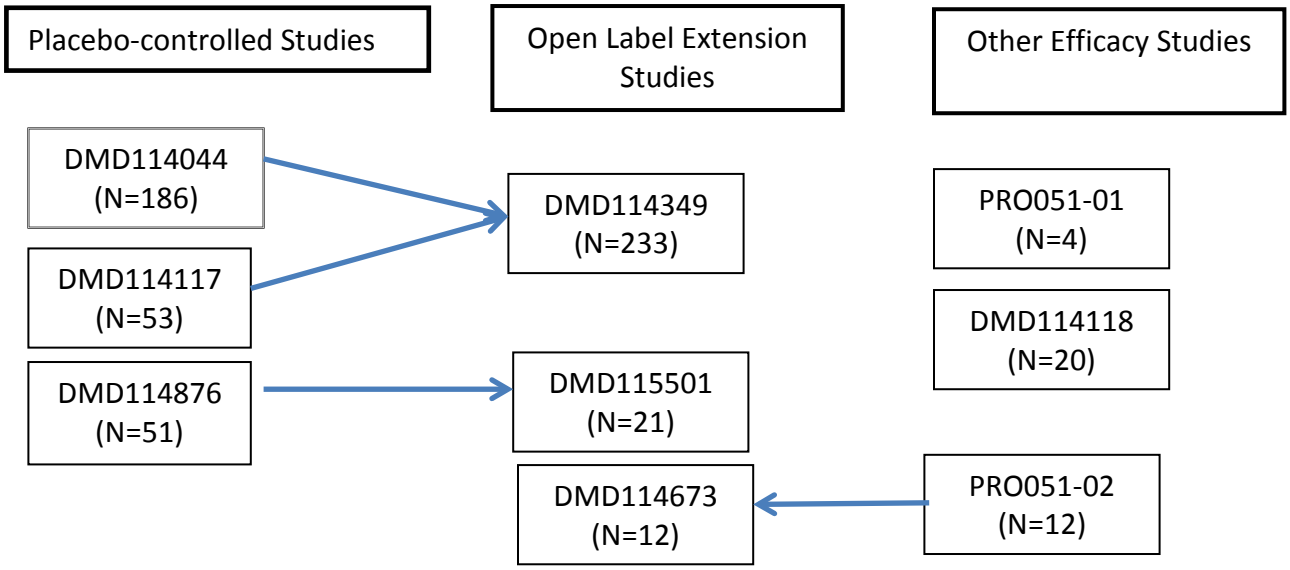
Not applicable.

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The drisapersen clinical development program consists of nine clinical studies in 326 boys with DMD (Table 1). Of the 326 subjects treated in the clinical development program, 312 received at least one dose of drisapersen. The cut-off date for the NDA submission was 31 August 2014. In September 2013 dosing was halted in all studies after the negative results of the Phase 3 Study DMD114044. No subjects received drisapersen from September 2013 up to the cut-off date. Seven clinical studies were completed by the cut-off date.

A schematic of the development program is shown below:



Clinical Review (Efficacy)
NDA 206, 031 (Drisapersen)

Table 1 Summary of clinical studies of drisapersen for the treatment of DMD

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
DMD 114117 Completed	Phase II Randomized, double-blind, placebo-controlled, parallel group	Loading dose: 6mg/kg SC drisapersen twice weekly for 3 weeks, then either: Continuous: SC 6 mg/kg/wk or Intermittent: alternating weeks of SC 6 mg/kg twice weekly and 6 mg/kg/wk for 6 weeks followed by 4 weeks off-dose period Dose–matched placebo	1°: 6MWD at week 24	48 weeks	N=53	ambulant subjects, 6MWD≥ 75m, able to Rise from floor ≤7s	13 centers in 9 countries
DMD 114876 Completed	Phase II Randomized, double-blind, placebo-controlled, parallel group	3 mg/kg/wk or 6 mg/kg/wk Volume-matched placebo	1°: 6MWD at Week 24	24 weeks (followed by 24-week post-treatment period with no treatment)	N=51	ambulant subjects, 6MWD≥ 75m, able to Rise from floor ≤15s	13 centers in 1 country
DMD 114044 Completed	Phase II Randomized, double-blind, placebo-controlled, parallel group	6 mg/kg/wk Dose–matched placebo	1°: 6MWD at Week 48	48 weeks	N=186	ambulant subjects, 6MWD≥ 75m	44 centers in 19 countries
Short-term Repeat-dose Open Label Study							
PRO051-02 Completed	Phase I/II Open-label, rising dose	0.5 mg/kg, 2.0 mg/kg, 4.0 mg/kg, or 6 mg/kg SC once weekly	1°: Dystrophin	5 weeks	N=12	ambulant and non-ambulant subjects	2 centers in 2 countries
Long-Term Extension Studies to Support Efficacy and Safety							
DMD	Phase I/II	6 mg/kg/wk drisapersen SC	6MWD	Ongoing	N=12	ambulant and non-	2 centers in 2

114673 (Extension to PRO051-02) Ongoing	Open-label uncontrolled extension of PRO051-02	for 72 weeks. After an interval of 8 weeks (Weeks 73-80) off drug, subjects restarted an intermittent treatment regimen of 6 mg/kg/wk drisapersen for 8 weeks, followed by 4 weeks off treatment (12-week cycles) up to 188 weeks. An IV sub study was conducted following Week 188		Planned: Until launch or termination of development. Actual: Dosing in the study was halted in September 2013, but was restarted after the data cut off for this submission (August 31, 2014).	IV sub study N=7	ambulant subjects at start of parent study PRO051-02	countries
DMD 114349 Terminated Completed	Phase III Open-label extension of DMD114117 and DMD114044	6 mg/kg/wk SC drisapersen Subjects with tolerability issues had the option to enter the intermittent arm of 6 mg/kg/wk for 8 weeks followed by 4 weeks off dose. Subjects who did not wish to receive drisapersen or who had to withdraw from both active arms during the study had the option to go into a natural history observation arm.	6MWD	Planned: Until launch or termination of development (minimum 104 weeks). Actual: Up to 101 weeks at time of termination of dosing in September 2013	N=233	ambulant at start of parent study (DMD114044 or DMD114117)	58 centers in 24 countries
DMD 115501 Ongoing (not submitted)	Phase III Open-label extension of DMD114876	6 mg/kg/wk SC drisapersen Subjects with tolerability issues had the option to enter the intermittent arm of 6 mg/kg/wk for 8 weeks followed by 4 weeks off		Planned: Until launch or termination of development Actual: Dosing in the study was halted in	N=21	ambulant at start of parent study (DMD114876)	13 centers in 1 country

		dose.		September 2013, but was restarted after the data cut off for this submission (August 31, 2014).			
Other studies pertinent to the review of efficacy or safety							
PRO051-01 Completed	Phase1 Open label, single dose	0.8 mg IM	Safety, tolerability Dystrophin	Single dose	N=4	Ambulant and non-ambulant	Single center
DMD 114118 Completed	Phase 1 Randomized, placebo-controlled, rising dose	3, 6, 9, 12 mg/kg SC No subjects received 12 mg/kg	Safety, tolerability, PK	Single dose	N=20	Non ambulant	2 centers in 2 countries

5.2. Review Strategy

I reviewed all the clinical efficacy data (placebo controlled studies, open label studies and the exploratory Phase I studies) submitted to the NDA along with the published literature and medical text books to evaluate the efficacy of drisapersen in the treatment of DMD with mutations amenable to exon 51 skipping. I conducted my own analyses of the primary data using graphical explorations and descriptive statistics in JMP, JReview and Excel. The applicant's primary statistical MMRM analyses were confirmed by the statistician Dr. Sharon Yan, Ph.D. I reviewed the dystrophin data from each study, but the methodology for the assessment of dystrophin and its reliability in each study was reviewed by Dr. Ashutosh Rao, Ph.D. His comments were incorporated in this review of the dystrophin data. The safety data were reviewed by Dr. Evelyn Mentari, MD in a separate review. The MRI data were reviewed by Dr. Daniel Krainak, Ph.D from CDRH Imaging Division.

6 Review of Relevant Individual Trials Used to Support Efficacy

Study DMD 114117

6.1.1. Study Design

Overview and Objective

Study DMD114117 was a Phase II placebo controlled clinical study to assess two dosing regimens, continuous and intermittent, of 6mg/kg drisapersen. An intermittent regimen was selected to potentially mitigate liver and kidney toxicities. PK/PD modeling predicted that the selected intermittent regimen would provide similar peak concentrations (Cmax) and total exposure (AUC) over the 48 weeks to the continuous regimen. Both the continuous and the intermittent regimen had comparable total doses administered throughout the study.
Studied period**:** 01 September 2010 to 12 September 2012
Study center(s): 13 centers in 9 countries in Australia, Belgium, France, Germany, Israel, Netherlands, Spain, Turkey, and the United Kingdom.

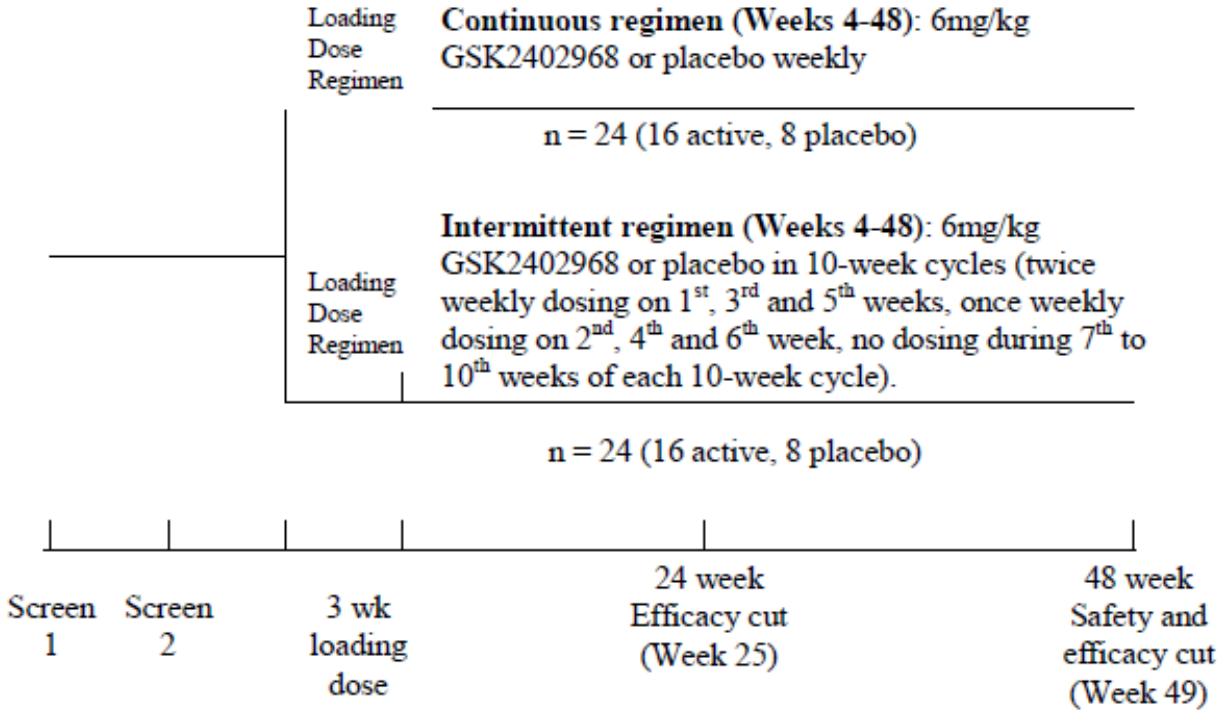
Trial Design

Study DMD114117 was a 48 week double-blind, parallel-group, placebo-controlled clinical study in ambulant DMD boys, with primary efficacy at 24 weeks. The study was fully blinded with respect to active and placebo in each cohort, however the different regimens were not fully blinded, due to the number of dummy doses that would be needed to blind both regimens.
At the end of the treatment period, subjects who completed the study had the option to enter an open-label extension study (Study DMD114349). Additional criteria for entering the open label study are discussed in section 6.4. If subjects did not enter the extension study, they were monitored for a minimum of 20 weeks after the last dose.

Study Schematic is shown in

Figure 3. Screen 1 and 2 were 4 and 2 weeks prior to randomization, respectively.

Figure 3 Study Design Schematic



Population: N=54 ambulant subjects with DMD resulting from a mutation that can be corrected by exon 51 skipping. The sample size was not based on statistical considerations, but would allow the detection of an effect size of 1.1 with 80% power at significance level of 5%

Key Inclusion Criteria:

- Mutation confirmed by a state-of-the-art DNA diagnostic technique covering all DMD gene exons, including but not limited to MLPA (Multiplex Ligation-dependent Probe Amplification), CGH (Comparative Genomic Hybridization) or H-RMCA (High-Resolution Melting Curve Analysis)
- Male of at last 5 years of age
- Able to rise from floor in ≤7 seconds (without aids/orthoses),
- Able to complete the 6MWD test with a distance of at least 75m,
- Results of 6MWD must be reproducible (within 20% for each test) between Screening Visits 1 and 2
- On glucocorticoids for a minimum of 6 months immediately prior to screening, with no significant change in total daily dosage or dosing regimen for a minimum of 3 months immediately prior to screening and a reasonable expectation that total daily dosage and dosing regimen will not change significantly for the duration of the study (unless clinically indicated)
- Life expectancy of at least 1 year

- QTc <450 (based on single or average QTc value of triplicate ECGs obtained over a brief recording period), or <480 msec for subjects with Bundle Branch Block. Note: QTc could be either QT interval corrected for heart rate by Bazett's formula (QTcB) or QT interval corrected for heart rate by Fridericia's formula (QTcF), and machine read or manual overread.

Key Exclusion Criteria:

- Any additional missing exon for DMD
- Current or history of liver or renal disease
- Use of anticoagulants, antithrombotics or antiplatelet agents, previous treatment with investigational drugs, idebenone or other forms of Coenzyme Q10, within 1 month of treatment initiation.
- Positive hepatitis B surface antigen, hepatitis C antibody test, or human immunodeficiency virus (HIV) test at screening,
- Symptomatic cardiomyopathy, to discuss with medical monitor, if subject has a left ventricular ejection fraction <45% at Screening

Key Withdrawal Criteria:

- AE jeopardizing safety of the subject
- Administration of idebenone or Coenzyme Q10 during study
- New evidence of cardiomyopathy.
- QTc>500, to be discussed with Medical Monitor

Dosing regimen:

After a 2-4 week screening period, all subjects received a loading dosing regimen of twice weekly subcutaneous (SC) dosing with 6 mg/kg drisapersen for the first 3 weeks, which was followed by the following regimen in parallel cohorts for 48 weeks. Each cohort included subjects on drisapersen and matched placebo in a 2:1 ratio. Subject randomization was done using Interactive Voice Response System according to the randomization schedule.

- Continuous regimen; 6 mg/kg SC drisapersen once weekly for 48 weeks
- Intermittent regimen; 6 mg/kg SC drisapersen twice weekly on 1st, 3rd and 5th weeks, once weekly on 2nd, 4th and 6th weeks, and no active drug on 7th to 10th week of each 10 week cycle for 48 weeks

Injection sites were rotated to minimize injection site reactions. Some subjects received multiple injections depending on the weight of the subject. There were no food restrictions with regards to dosing. All study treatment was supplied in identical vials. The appearance of the active and placebo solutions were not identical and hence a blinding label was applied to the syringe to minimize the risk of unblinding the subjects. The volumes were different according to the weight of the subject, and were matched for active and placebo. To maintain the blind, the dose was prepared and administered by appropriately trained and qualified unblinded personnel who were not involved in the study's efficacy assessments.

Reviewer's Comment:

Applicant's study design elements mostly appeared reasonable based on the preclinical and clinical information available at the time of study conduct as discussed below:

- **Design:**
  - **Approaches towards blinding of active and placebo treatment were "less than ideal" by design. The placebo solution had a different appearance from the drisapersen solution. The study, by design, was not blinded for the regimens, with a different schedule of doses for the continuous and intermittent arms. Treatment was administered by personnel who knew if drug or placebo was being administered; while these personnel were not involved in efficacy assessments, direct patient contact (and presumably contact with other study personnel) may have jeopardized blinding.**
- **Inclusion/Exclusion Criteria:**
  - **Steroids are the standard of care in the treatment of DMD; therefore enrolling subjects on their stable steroid dose was prudent, but there are many factors associated with steroid use that would render heterogeneity to the selected DMD population. The enrollment criteria required subjects on steroid for a minimum of 6 months, hence some subjects were on steroid for much longer and these subjects may have different disease progression trajectories (Kim, 2014). At this time there is no consensus on the optimal dose, regimen (continuous or intermittent) or the type of steroid. The choice of steroids also varies from country to country. Published data suggest that earlier initiation of steroids provide more sustained improvement in clinical function (Moxley RT III, 2005; Manzur, 2008). Recent 36 month data have shown that patients on daily steroids do better than intermittent steroids (Pane 2014). The impact of age of initiation of steroid use on disease progression is not well established, but in general DMD patients receiving steroid treatment increase ambulation from 2-5 years compared to those not on steroid treatment. All these factors were not controlled in the selection of patients for this study. Understandably, the standard of care being different from country to country enrolling patients with regards to consistency with steroid use would considerably limit the patients meeting the enrollment criteria. These factors are likely to impact the disease trajectory of an individual patient.**
  - **The inclusion criteria required subjects to have no more than 20% difference in 6MWD at the two screening visits 1 and 2 that were separated by 2 weeks. This allows for a lot of variation in the 6MWD that is in fact larger than the difference possibly seen in 1 year in many cases.**
  - **The inclusion criteria of 75 m 6MWD would include subjects that are likely to lose ambulation in 1 year (Mazzone 2011). This criterion was based on available natural history data at the time of study conduct. Recent published data suggest that patients with 6MWD<325 are more likely to lose ambulation in 1 year (McDonald 2013b).**
  - **The inclusion criteria of rise of floor of ≤7 seconds was included for a more homogenous population, although disease trajectories may vary in subjects with rise from floor of <4 or >4 as well. In addition Rise from Floor in conjunction with 6MWD also appears important in disease progression (Mazzone 2010).**
  - **The impact of use of idebenone or other forms of Coenzyme Q10 more than 1 month of treatment initiation in not well established, but may add to variation in disease progression. Other enrollment criteria appear reasonable.**
- **Dose:**

- **A loading dose appears appropriate. PK modeling had suggested that steady state could be achieved 6 weeks earlier with a loading dosing regimen of twice weekly dosing for 3 weeks, given the long half-life of drisapersen (29 days).**
- **There is limited human data on a 9mg/kg /week dose in non-ambulant subjects, but decision was based on pre-clinical pro-inflammatory findings. Applicant has not evaluated longer dose interval with higher doses due to limitations in injectable volume by SC administration.**

- **Assessments:**
  - **Based on what was known at the initiation of this study, efficacy assessments at 24 and 48 week seemed reasonable. PK/PD characteristics of drisapersen had estimated dystrophin protein turnover half-life of 5 weeks. Based on this it was hypothesized that dystrophin expression will reach steady state in 24 weeks, hence a 24 week primary endpoint. Efficacy was also assessed at 48 weeks. (The dystrophin half-life was verified by the sponsor during the review cycle. The Applicant clarified in a response dated June 18, 2015 that this reflected the thought at the time protocol was written. Recent published studies suggest a dystrophin half-life in the range of 2 to 4 months in the skeletal muscle of mdx mice (Verhaart 2014; Wu, 2012). Although, the dystrophin half-life from mice may not predict human dystropin half-life, but likely is longer in humans than in rodents. Given this, studies longer than 48 weeks may be desirable to achieve optimal results to allow adequate time for the attainment of steady state levels of dystrophin.**

Study Endpoints

The following efficacy assessments were done once or twice at screening, baseline, and Weeks 13, 25, 37 and 49, unless specified otherwise.

Primary efficacy endpoint:

- **Muscle function using 6 minute walking distance (6MWD) test**: change from baseline at 25 weeks. Subjects were asked to walk, as quickly but as safely as they could, up and down a fixed distance until they were told to stop after 6 minutes. The subjects were warned of the time and were told that they could stop earlier if they felt unable to continue walking. The total distance walked within 6 minutes (or until the subject stopped in case of early termination of the test) was recorded in meters.

Secondary efficacy endpoints:

- **Timed function tests (times and grading**): These were assessed on a 6-point scale to differentiate those subjects with similarly fast times who may have achieved a ceiling time (Attached to the Appendix A).
  - **Rise from floor**, no aids or orthoses allowed, subjects stood from a standardized supine position as quickly as possible when told to "go". Time was recorded from initiation of movement to upright position.
  - **10m walk/run**, no aids or orthoses allowed: Subject was asked to walk a 10 m measured walkway as quickly as possible. Time was recorded to one tenth of a second. If the subject could not complete the 10-meter walk, the total distance was recorded.
  - **4-stair climb (ascend and descend)**, handrail allowed: subject ascended and descended 4 steps
- **North Star Ambulatory Assessment**: It consists of 17 activities graded 0 (unable to perform), 1 (performs with modifications), 2 (normal movement). NSAA Total Score ranges from 0 to 34, with a

score of 34 implying normal function. The scale assesses activities required to remain functionally ambulant (e.g. rise from the floor), activities that can be difficult even early in the disease (e.g. standing on heels) and activities that are known to progressively deteriorate over time (stand from a chair, walk). (Scale attached in the Appendix A).

- **Muscle strength (total score):** knee flexors, knee extensors, elbow flexors, elbow extensors, shoulder abductors and hip flexors (as determined by handheld myometry using a microFET2 myometer)
- **Frequency of accidental falls during 6MWD**
- **Time to loss of ambulation**
- **Pulmonary function using non-invasive spirometry** (FEV1, FVC, MIP, MEP, PCF, PF)
- **Creatine kinase serum concentrations**: at Screening, baseline and Weeks 3, 5, 9, 13, 17, 21, 25, 33, 41 and 49.
- **Dystrophin expression** (muscle biopsies from tibialis anterior) including percent change from baseline: at baseline, Week 25 and 49 and mRNA production in muscle tissue

Exploratory endpoints:

Pediatric Quality of Life Neuromuscular module, gait characterization by accelometry during 6MWD, percent predicted 6MWD (the percentage of the predicted 6MWD for a healthy boy of the same age and height that the boy with DMD was able to walk), lean body mass by DEXA scan, were conducted as exploratory endpoints. Pharmacokinetics, drisapersen muscle concentration and DNA samples were also taken.

Reviewer's Comment:

6MWD is an effort dependent endpoint. The results may be affected by bias from unblinding due to adverse events such as injection site reaction, which occurred in most patients administered drisapersen. 6MWD was considered a reasonable clinical endpoint in DMD, as little was known on the natural history data of 6MWD in DMD and most data were published on the validity of 6MWD in DMD.

Like the 6MWD, the Timed Function Tests and NSAA are also effort and motivation dependent and measure similar functional capabilities as the 6MWD. In addition, NSAA scoring may be subjective and susceptible to observer bias.

Statistical Analysis Plan

The intent-to-treat (ITT) population was defined as all subjects who are randomized to the study and received at least one dose of study medication and have at least one efficacy assessment. This is the primary population for evaluation of efficacy parameters. The per protocol (PP) population is defined as all ITT subjects and have no major protocol deviations.

There was no interim analysis, although two main analyses were done (1) at week 25 (primary) and (2) at week 49.

Primary Endpoint Analyses: Primary assessment of efficacy data was conducted using a Mixed Effect Model Repeated Measure (MMRM) at week 25 on the Observed case (OC) data. The model included

treatment, visit, treatment by visit interaction, country/country grouping, baseline 6MWD and baseline 6MWD by visit as fixed effects. Comparison of each dosing regimen with placebo (combined group pre-specified) was adjusted using Bonferroni-Holm adjustment for multiplicity. The p-values from the two primary analyses (6 mg/kg drisapersen continuous vs. placebo, and 6 mg/kg drisapersen intermittent vs. placebo), were ordered smallest to largest. The smallest p-value was compared to a significance level of $\alpha/2$ (0.025). If the result was demonstrated to be statistically significant at this level, i.e. $p<0.025$, then the second p-value was compared to a significance level of α (0.05). If the initial comparison shows the result not to reach statistical significance, then the second comparison was also considered not to have reached statistical significance.
If the assumptions of normality were not met, a log-transformation of the data prior to an MMRM analysis was used.
Sensitivity Analyses for primary endpoint: The following sensitivity analyses were performed:

- ANCOVA on OC data for the ITT population
- ANCOVA on LOCF data (missing data for at least 3 months) for the ITT population
- ANCOVA on data imputed via multiple imputations for the ITT population
- MMRM on OC data with PP population

ANCOVA model included fixed terms for treatment, baseline 6MWD and country. The covariates assessed were county, baseline 6MWD, steroid regimen, age, baseline rise time, lean body mass index.
MMRM model included terms for Treatment, Visit, Treatment by Visit, Country Grouping, Baseline 6MWD and Baseline 6MWD by Visit.

<u>Secondary endpoint analyses:</u>

- For continuous endpoints MMRM analyses on OC data, with similar fixed terms
- Kaplan-Meir and Log rank test on time to event endpoints such as loss of ambulation (if ≥4 subjects in either treatment group experienced a loss of ambulation)
- ANCOVA on %predicted 6MWD on OC data

Protocol Amendments

The protocol amendments related to efficacy assessments are summarized below:

Amendment 1 (20 Jul 2010)	Country specific: To remove DEXA scan due to logistics
Amendment 2 (24 Sep 2010)	Country specific: to add conduct gait characterization collected by accelerometric data ta 5 sites (N=20 of 54 subjects) and include 50 healthy control height matched subjects for this.
Amendment 3* (13 Oct 2010)	• Approval of recruitment of healthy control was not granted, hence removed. Intent to enroll in a different protocol. • Removed the inclusion criteria that required reproducibility of Rise From Floor (within 20% at pre-drug visit 1 and 2). • Modified the exclusion criteria regarding concomitant medications: idebenone and Coenzyme Q allowed within 1 month of study administration instead of 6 months • Removed muscle biopsy at 49 weeks • 'Pediatric Quality of Life Neuromuscular module' moved from secondary endpoint to exploratory analyses.
Amendment 4*	• addition of the frequency of accidental falls during the 6MWD and time to

(19 Jul 2010)	loss of ambulation as 2° endpoint

*Also amended safety monitoring and stopping criteria

Reviewer's Comment: These amendments are unlikely to bias the study results as were done within the first month of study initiation when few subjects were enrolled.

Data Quality and Integrity: Sponsor's Assurance

The study was conducted in accordance with ICH GCP (ICH E3 and E6) and applicable country-specific requirements. Written commitments were obtained from investigators to comply with GCP. Study was conducted with written informed consent from subjects and their parents.

6.1.2. Study Results

Patient Disposition

A total of 53 subjects were randomized (Table 2). No subject withdrew from the study.

Protocol Violations/Deviations

The number of subjects with protocol deviations is summarized in Table 2.

Table 2: Number of subjects (%) with major protocol deviations up to week 25

ITT and Safety Population	Placebo (combined) (N=18)	6 mg/kg Drisapersen Continuous (N=18)	6 mg/kg Drisapersen Intermittent (N=17)	Total (N=53)
PP Population	17 (94)	17 (94)	15 (88)	49(92)
Subject with major protocol deviation	1(6)	1(6)	2(12)	4(8)
Failed Inclusion criteria (Able to complete the 6MWD test with a distance of at least 75 m and results of 6MWD within 20% of each other at each pre-drug visit.)[a]	1(6)	1(6)	1(6)	3 (6)
Failed Inclusion criteria (Receiving glucocorticoids for ≥ 6 months prior to screening, with no significant change in total daily dosage or dosing regimen for 3 months prior to screening.)[b]	0	0	1(6)	1(2)

Source: NDA DMD114117 study report, page 58

[a]Subject 3055 in the placebo group, Subject 2129 in the 6 mg/kg drisapersen continuous group and Subject 2126 in the 6 mg/kg drisapersen intermittent group. [b]Subject 2103 in the 6 mg/kg drisapersen intermittent

Subject 3055 in the placebo group in addition to not being able to complete the 6MWD test with a distance of at least 75 m at screening also had a single deletion of exon 45 that was not amenable to exon 51 skipping. Given the fact that this subject was on placebo, the applicant included him in the primary analysis with the ITT population. In addition, two placebo subjects on a single visit (week 37 and week 9, respectively) were given active drug based on PK analysis). One subject had lower

drisapersen concentrations at week 9 and according to the applicant probably missed a dose that was not reported.

Reviewer's Comment:

- **The sensitivity analysis (MMRM with the PP population) was also positive with a similar p-value (p=0.013); hence the impact of protocol violation of subject 3055 was not a concern.**
- **Dr. Sharon Yan (Statistician) also conducted an analysis averaging the 2 screening and baseline 6WMD values. A treatment difference over placebo of 30m (p=0.03) was obtained from the drisapersen continuous regimen. Hence, the impact of protocol violation in a few subjects with 6MWD for the 2 screening visits not within 20% was not a concern.**
- **A single missed dose or wrong treatment on a single occasion is unlikely to affect efficacy results, but analysis was done excluding these subjects as well.**

Table of Demographic Characteristics

According to the applicant, the demographic characteristics were similar across treatment groups with the intermittent group being older and having slightly higher mean height and weight values. The demographic characteristics for primary analysis are shown in Table 3.

Table 3 Demographic characteristics of the primary efficacy analysis

	Placebo (combined) (N=18)	6 mg/kg Drisapersen Continuous (N=18)	6 mg/kg Drisapersen Intermittent (N=17)	Total (N=53)
Age (yrs)				
Mean (SD)	6.9 (1.2)	7.2 (1.7)	7.7 (1.5)	7.3 (1.5)
Median	7.0	6.5	8.0	7.0
Min., Max.	5, 9	5, 11	5, 10	5, 11
Ethnicity, n (%)[a]				
n	16	17	15	48
Not Hispanic/Latino	16 (100)	17 (100)	14 (93)	47 (98)
Hispanic/Latino	0	0	1 (7)	1 (2)
Race, n (%)[a]				
n	16	17	15	48
White - White/Caucasian/ European Heritage	13 (81)	15 (88)	14 (93)	42 (88)
White - Arabic/North African Heritage	0	2 (12)	0	2 (4)
American Indian or Alaska Native	0	0	1 (7)	1 (2)
Asian - South East Asian Heritage	1 (6)	0	0	1 (2)
Native Hawaiian or other Pacific Islander	1 (6)	0	0	1 (2)
Mixed Race	1 (6)	0	0	1 (2)

Height (cm)				
Mean (SD)	119 (8)	118 (11)	121 (10)	NA
Median	120	120	120	NA
Min., Max.	99, 132	102, 139	106, 139	NA
Weight (kg)				
Mean (SD)	25 (5)	25 (7)	28 (10)	NA
Median	24	23	26	NA
Min., Max.	16, 35	16, 42	18, 51	NA

Source: DMD114117 study report, page 60

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

According to the Applicant, baseline DMD characteristics were relatively balanced across treatment groups (Table 4). The time since first symptoms, diagnosis and first corticosteroid use in the intermittent group were slightly longer than the other two treatment groups which are consistent with the older mean age of this group. Mean baseline values for the 6MWD test were higher in the continuous group (427.61 m) than in the placebo (403.18 m) and intermittent (394.57 m) treatment groups.

Table 4 Baseline disease characteristics

	Placebo (combined) (N=18)	6 mg/kg Drisapersen Continuous (N=18)	6 mg/kg Drisapersen Intermittent (N=17)	Total (N=53)
Time Since First Symptoms (months)				
Mean (SD)	63 (24)	61 (25)	64 (24)	63 (24)
Median	73	57	63	62
Min, Max	15, 95	27, 112	27, 105	15, 112
Time Since Diagnosis (months)				
Mean (SD)	44 (22)	45 (28)	48 (26)	45 (25)
Median	35	41	47	43
Min, Max	12, 82	3, 96	3, 105	3, 105
Time Since First Corticosteroid Taken (months)				
Mean (SD)	24 (14)	26 (21)	33 (17)	27 (18)
Median	22	14	34	26
Min, Max	7, 60	7, 69	7, 63	7, 69
Corticosteroid Regimen				
Continuous	11 (61)	12 (67)	9 (53)	32 (60)
Intermittent	7 (39)	6 (33)	8 (47)	21 (40)
6MWD (m)				
Mean	403	428	395	NA
(SD)	(45)	(70)	(67)	
Exon Mutation, n (%)				

DMD 45-50 deletion	7 (39)	6 (33)	5 (29)	18 (34)
DMD 48-50 deletion	3 (17)	6 (33)	6 (35)	15 (28)
DMD 49-50 deletion	1 (6)	4 (22)	3 (18)	8 (15)
DMD 50 deletion	4 (22)	1 (6)	3 (18)	8 (15)
DMD 52 deletion	3 (17)	1 (6)	0	4 (8)

Source: NDA DMD114117 study report, page 61

Reviewer's Analysis and Comments on Baseline Characteristics:

The heterogeneity in the DMD population is well known (Humbertclaude 2012, McDonald 2013). Some advantage for 6mg/kg/week group was observed. Higher baseline function is almost always associated with slower long term decline (McDonald: http://www.treatnmd.eu/downloads/file/meetings/2013/workshop/Session1/McDonald_NH.pdf

Subjects in the continuous treatment regimen appeared to have greater number of subjects that were < 7 years, on continuous steroids, higher mean baseline 6 MWD, greater number of subjects with baseline 6MWD of >400m, shortest time since first symptoms that is consistent with a younger more functional population that are all likely to have a slower decline, even though the average age was slightly higher for the continuous treatment. In addition, I looked for other disease characteristics that would enable the assessment of functional capabilities at baseline. Greater number of subjects on continuous treatment could jump with both feet up at the same time, hop with clearing foot and heel from floor at the same time, rise from floor <4 seconds and had the ability to rise from floor without gower's maneuver. These are considered milestones that can predict loss of ambulation (McDonald). The percentage of subjects across the treatment groups are shown in Table 5, suggesting subjects in the 6mg/kg/week group have higher functional capabilities and likely to have a slower decline in the 6MWD. The randomization was conducted as per the master randomization schedule generated via an interactive voice response system. Hence, these differences in treatment groups occur by random chance.

Table 5 Percentage of subjects with Baseline Characteristics

Baseline Factors	Continuous 6mg/kg/week	Intermittent 6 mg/kg/week	Placebo
Age <7 years	50%	30%	39%
6MWD>400m	61%	41%	50%
Rise From Floor <4 secs	44%	18%	22%
On continuous regimen	67%	53%	61%
Other factors: Ability to jump with both feet up at the same time	100%	88%	77%
Ability to hop with clearing foot and heel from floor	50%	29%	27%
Ability to rise from floor without gower's maneuver	27%	6%	11%

Interaction between treatment and baseline 6MWD, age and steroids in a statistical model did not lead to any statistically significant interaction, but the study size is small and not powered to show any differences due to covariates.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

No imbalances in concomitant medications were noted. All subjects were 80% to 120% compliant with dosing. The median dose (in mg) was the lowest in the continuous drisapersen treatment arm. These exposure differences likely arise due the higher % of younger kids in the continuous treatment arm as dosing is based on mg/kg. The duration of exposure was similar across treatment arms.

Efficacy Results – Primary Endpoint

Applicant's Primary Analysis and conclusions:
Based on the primary efficacy MMRM analysis for change from baseline in 6MWD at Week 25, there was a statistically significant treatment benefit for the continuous regimen [35 m; p=0.01 (p<0.025)] over placebo, but not for the intermittent regimen (Table 6). A similar analysis was also done at week 49. A treatment differences between drisapersen and placebo of 36 m and 27 m were observed for the continuous and intermittent groups respectively at Week 49. The continuous group showed some decline towards baseline after the initial increase in 6MWD up to Week 25, whereas the intermittent group was relatively stable over the 48 week time-period (Table 6).
Note: After Week 25, the biostatistics and programming team was unblinded, but the subjects, investigators and monitors were blinded. There was also a blinded, independent Medical Monitor assigned to the study from the point of unblinding for the Week 25 analysis, to maintain the integrity of medical decisions.

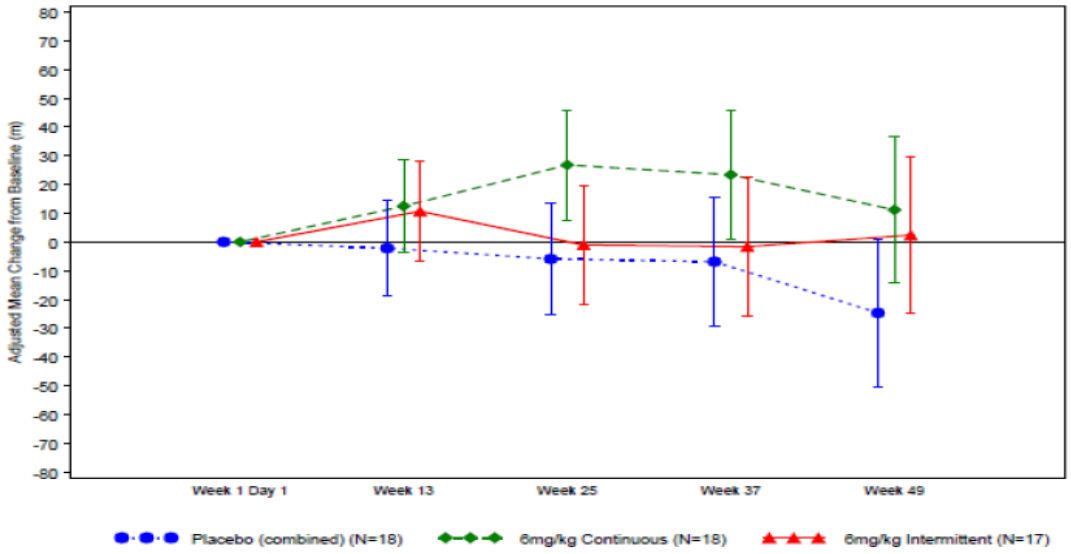
Table 6 Summary of MMRM Analysis of Change from Baseline in 6MWD (m)

	Placebo (combined) (N=18)	6 mg/kg Drisapersen Continuous (N=18)	6 mg/kg Drisapersen Intermittent (N=17)
Baseline			
n	18	18	17
Mean (SD)	403 (45)	428 (70)	396 (70)
Week 25			
n	16	16	15
Adjusted mean change (SE)	-4 (10)	31 (10)	-0.1 (10)
Adjusted mean difference vs. placebo		35	4
95% CI		(8, 62)	(-24, 31)
p-value		0.01	0.80

Week 49			
n	17	18	15
Adjusted mean change (SE)	-25 (13)	11 (13)	2 (14)
Adjusted mean difference vs. placebo		36	27
95% CI		(-0.11, 72)	(-10, 64)
p-value		0.05	0.15

Source: DMD114117 study report page 64

Figure 4 MMRM Analysis of Change from Baseline in 6MWD (m) at Week 49



Source: Study DMD114117 Study Report page 68

Interactions between treatment and age, baseline rise from floor, baseline lean body mass, baseline 6MWD, corticosteroid regimen and country grouping at week 25 showed only a statistically significant interaction ($p \leq 0.10$) for baseline rise from floor. The confidence interval was larger, so the applicant cautions the interpretation of this. In addition, the study size is small.

Reviewer's Comment: Note that not all subjects were included in the primary analysis at Week 25, since five subjects had their 6MWD assessment done at Week 24 and one subject at Week 27. A sensitivity analysis including these subjects gives a p value of 0.02 with a treatment difference of 31m for the continuous regimen compared to placebo (Table 7).
The analysis at Week 49 was not a planned analysis and cannot be evaluated while controlling type 1 error.

Applicant's Sensitivity Analyses for the primary endpoint: The planned sensitivity analyses supported the primary analysis as shown in Table 7. Sensitivity analyses at week 49 support the MMRM analysis at week 49 (not shown in Table).

Table 7 Sensitivity analyses on change from baseline 6MWD at week 25 for drisapersen continuous regimen

Analysis	Population	Dataset	Treatment Difference	95% CI	P-value
MMRM	PP	OC	38	(8, 68)	0.01
ANCOVA	ITT	OC	35	(7, 63)	0.01
ANCOVA	ITT	LOCF	31	(4, 57)	0.03
MMRM	ITT	OC (unslotted)[a]	31	(5, 58)	0.02
MMRM	ITT	OC (exc. outlier)[b]	31	(4, 58)	0.03
MMRM, Uncombined Placebo	ITT	OC	47	(12, 82)	0.01

Source: DMD114117 study report, page 66

a. For reporting purposes, efficacy data were slotted to pre-defined visit windows, based on the time of the assessment since first dose. Where a visit was attending particularly early or late, the assessment would have fallen outside of the visit window and was thus excluded from analyses. This analysis of unslotted data, analyzed the data according to the investigator recorded visit, regardless of the time at which this occurred.

b. Subject 3002, randomized to placebo intermittent was determined to be an outlier by the applicant (6MWD of 322 m, 432.2 m and 265 m at Baseline, Week 13 and Week 25 respectively): gained 110 m at Week 13.

Additional Analyses on 6MWD:

1. MMRM analyses with placebo groups analyzed separately (continuous and intermittent placebo): The treatment difference for the continuous regimen compared to continuous placebo was 47m. The placebo continuous and placebo intermittent performed differently (Table 8). The applicant is unclear of the difference in placebo response in the two regimens, but explains that this could be due to chance due to small group size combined with inherent inter-subject variability (including age).

Table 8: MMRM analyses with placebo groups analyzed separately

	Placebo Continuous (N=9)	Placebo Intermittent (N=9)	6 mg/kg Drisapersen Continuous (N=18)	6 mg/kg Drisapersen Intermittent (N=17)
Baseline				
n	9	9	18	17
Mean (SD)	406 (49)	400 (43)	428 (70)	395 (70)
Week 25				
n	7	9	16	15
Adjusted mean change (SE)	-15 (14)	6 (13)	32 (10)	0.3 (10)
Adjusted mean difference vs. placebo			47	-6
p-value			0.01	0.72
Week 49				
n	9	8	18	15
Adjusted mean change (SE)	-36 (18)	-13 (18)	11 (13)	3 (13)
Adjusted mean difference vs. placebo			47	16
p-value			0.04	0.48

Source: NDA DMD114117 study report, page 69

2. MMRM analysis in combined drisapersen regimens (continuous and intermittent combine):
No statistically significant difference (p=0.12) was observed at Week 25 when the two drisapersen treatment regimen groups were combined, but a nominal p-value of 0.05 was observed at Week 49 (Table 9).

Table 9 MMRM analyses of the combined drisapersen regimens

	Placebo (combined) (N=18)	6 mg/kg Drisapersen (combined) (N=35)
Week 25		
n	16	31
Adjusted mean change (SE)	-3 (10)	16 (7.4)
Adjusted mean difference vs. placebo		20
95% CI		(-5, 44)
p-value		0.12
Week 49		
n	17	33
Adjusted mean change (SE)	-25 (13)	7 (9)
Adjusted mean difference vs. placebo		31
95% CI		(0.5, 62)
p-value		0.05

Source: NDA DMD114117 study report, page 71

3. Change from baseline in 6MWD by response category:
Response was measured as the percentage of subjects that achieved a fixed change in 6MWD (≥-30 m, ≥0 m, ≥30 m, ≥60 m or ≥-10%, ≥0%, ≥10%, ≥20% and≥30% change). Subjects could be included in more than 1 category. There were 19% subjects in the placebo and 38% drisapersen continuous arm and 20% in the intermittent arm that showed ≥ 30 m change in 6MWD at Week 25. A total of 31% subjects (n=5) in the drisapersen continuous arm and 13% (n=2) in the placebo group showed a ≥10% change in 6MWD.
4. Change from baseline in percent-predicted 6MWD
As 6MWD distance is influenced by age and development, analysis of the percent-predicted 6MWD that takes these factors into account were conducted (Henricson 2012). The percent-predicted 6MWD in DMD provides an estimate of performance relative to a healthy control population. An increase in the percent-predicted 6MWD is consistent with functional improvement. A treatment benefit (~6% difference) in favor of the continuous group over placebo was observed at both Week 25 (p=0.01) and Week 49 (p=0.05). The treatment difference over placebo with the intermittent regimen was 0.7% at Week 25 (p=0.78) and 5% at Week 49 (p=0.14).

Applicant's post-hoc analyses:

- MMRM analysis in subjects ≤7 years and > 7 years DMD:

The 6MWD generally improves in boys until the age of 7 years (Henricson 2012). The sponsor's analysis showed a treatment benefit of 77 m in >7 years at Week 25 compared to 22 m for boys ≤7 years for the continuous regimen.

Reviewer's Comment: The sample size is too small for any interpretable subgroup analysis of age in this study.
A post-hoc analysis, when combining the patients on continuous and intermittent shows a treatment difference in favor of drisapersen at each time point and statistically significant p of 0.05 at Week 49. Combining the treatments appears reasonable as they have the same drug exposure at Week 49. This may suggest treatment benefit at Week 48, given a more heterogeneous population.

Data Quality and Integrity – Reviewers' Assessment

There are no issues with data integrity.

Durability of Response

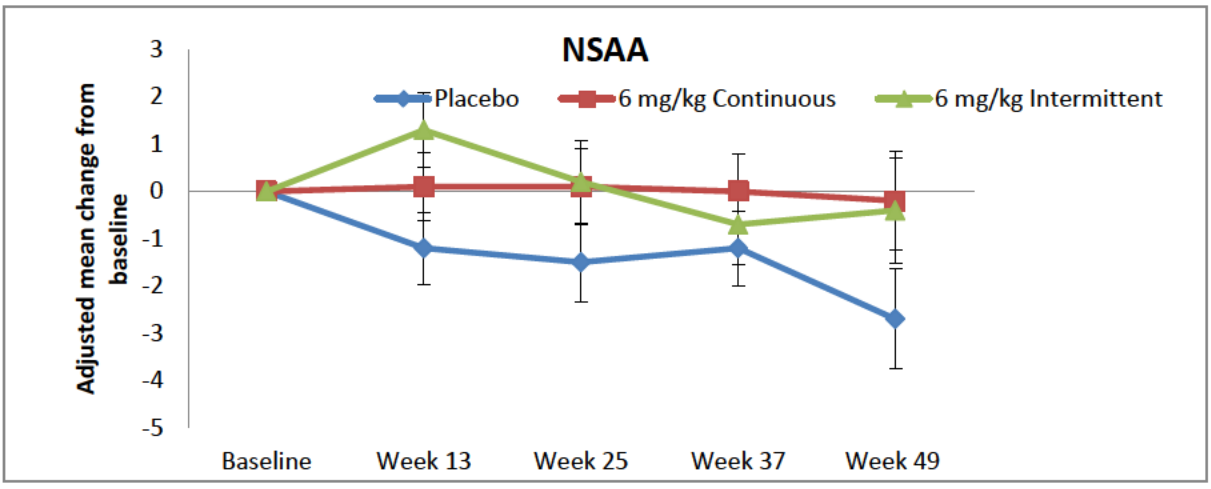
The treatment difference of 35 m for the continuous drisapersen regimen is maintained for the 49 weeks. This is probably because the placebo declines more at Week 49, such that the effect size remains the same at Week 48. For the continuous arm, the change from baseline in 6MWD declines after Week 25. It is unclear if this is due to the variability in the measure or a true treatment effect (Figure 9).

Efficacy Results – Secondary and other relevant endpoints

Applicant's key conclusions:

- None of the secondary endpoints showed a statistically significant treatment difference from placebo at Week 25 or 49 (Table 11, Week 49 summary). The frequency of worsening was variable and greater at Week 49 for most endpoints.
  - **Timed Function Tests (rise from floor, 10 m walk/run, and 4-stair climb/descent**):
    - The primary efficacy was supported by directionally favorable trends (non-significant) for the continuous group compared with placebo at Week 25 and 49 (Table 11) for Timed Function Tests
    - The intermittent regimen showed inconsistent and variable results for different timed functions tests at Week 25, but a trend favoring treatment at Week 49.
  - **NSAA**: Both treatment groups showed a favorable treatment difference relative to placebo in NSAA total scores, which was more pronounced at Week 49. The applicant states that when assessed against natural history, the differences between drisapersen and placebo at 49 weeks (continuous, 2.50; intermittent, 2.29) appear to be clinically meaningful.

Figure 5 MMRM Analysis of change from baseline for NSAA at each visit



- **Muscle Strength and Pulmonary Function Tests:** Small decrease from baseline in mean total muscle strength was observed in the continuous and intermittent treatment groups, compared to an increase in the placebo group at Week 25. At Week 49, small improvements in mean total muscle strength was observed in the continuous group, but the intermittent group muscle strength remained similar to that at baseline and overall still worse than placebo.
  The variable small changes in pulmonary function tests were similar across treatment groups.
- **PedsQL neuromuscular module questionnaire:** PedsQL showed a trend for improvement (higher scores indicating better quality of life) for the continuous group compared with placebo but not for the intermittent regimen (Table 10).

Table 10 Summary of Change from Baseline in PedsQL Total Score for both regimens

Assessor	Change from Baseline in PedsQL Total Score					
	Placebo (combined) (N=18)		6 mg/kg Drisapersen Continuous (N=18)		6 mg/kg Drisaperse n Intermittent	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Child						
Baseline	18	80 (10)	18	78 (9)	16	82 (10)
Change from Baseline at Week 25	17	-4 (11)	17	4 (6)	15	-4 (10)
Change from Baseline at Week 49	17	0.4 (12)	18	7 (9)	13	-0.2 (8)
Parent						
Baseline	18	76 (11)	18	78 (11)	17	77 (14)
Change from Baseline at Week 25	18	-2 (5)	18	-0.9 (7)	16	-3 (6)
Change from Baseline at Week 49	18	-4 (12)	17	0.3 (7)	15	-2 (7)

Source: Adapted from Study DMD114117 Study Report
Note: The PedsQL total score ranges from 0 to 100, where higher scores indicate better health-related QoL

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Table 11: Secondary Endpoints at week 49

Treatment	n	Baseline Mean (SD)	Adj. Mean Δ from Baseline (SE) at Week 49	Treatment Difference	95% CI	p-value
NSAA Total Score						
Placebo Drisapersen 6 mg/kg/wk	17 18	26 (4.4) 27 (4.5)	-2.7 (1.1) -0.2 (1.0)	2.5	(-0.4, 5)	0.09
4 Stair Climb Ascent Velocity (stairs/s)						
Placebo Drisapersen 6 mg/kg/wk	17 18	3.5 (1.6) 3.1 (1.2)	1.0 (0.5) 0.8 (0.5)	-0.2	(-1.7, 1.2)	0.72
10 m Walk/Run Velocity (m/s)						
Placebo Drisapersen 6 mg/kg/wk	17 18	5 (0.8) 5 (1.2)	0.8 (0.3) 0.1 (0.3)	-0.7	(-1.3, 0.05)	0.07
Rise from Floor (s)c						
Placebo Drisapersen 6 mg/kg/wk	17 18	5 (1.0) 5 (1.7)	3.8 (1.2) 0.9 (1.2)	-3	(-6.2, 0.4)	0.08
4 Stair Climb Descent Velocity (stairs/s)						
Placebo Drisapersen 6 mg/kg/wk	17 18	3 (0.9) 3 (0.7)	0.3 (0.4) 0.0 (0.4)	-0.3	(-1.5, 0.8)	0.57
Muscle Strength Total Score (lbs)						
Placebo Drisapersen 6 mg/kg/wk	17 18	122 (28) 124 (23)	7.5 (5) 5.9 (5)	-1.6	(-15, 12)	0.82

Source: Adapted from Study DMD114117 Study Report

- **Serum Creatine Kinase:**

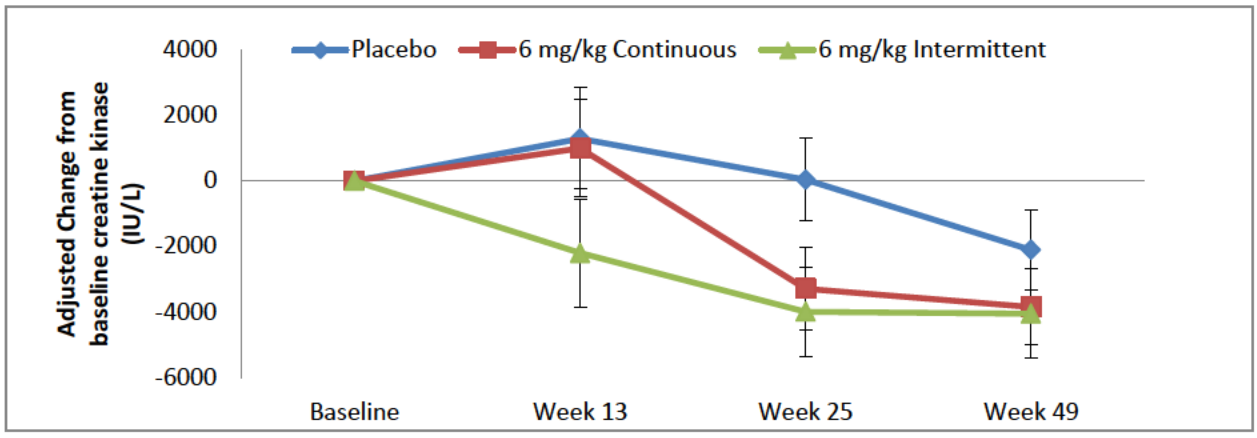
In early stages of DMD, increased muscle cell permeability (due to absence of dystrophin and increased membrane fragility) causes muscle specific enzymes such as creatine kinase to leak out of the cell. It is hypothesized that an improved membrane integrity induced by production of dystrophin can result in reduction of serum CK. At Week 25, there was a decline in CK for both drisapersen treatment arms compared with placebo, with a slightly greater treatment difference for the intermittent treatment group than the continuous treatment group. At Week 49, there was a trend of CK decline in both drisapersen arms compared with placebo, though the effect was smaller at Week 49 compared to Week 25 (Figure 6).

Table 12 Summary of MMRM Analysis of Change from Baseline in Creatine Kinase Serum Concentration (IU/L)

	Placebo (combined) (N=18)	6 mg/kg Drisapersen Continuous (N=18)	6 mg/kg Drisapersen Intermittent (N=17)
Baseline			
n	18	18	17
Mean (SD)	9525 (5415)	12267(6297)	14023 (7561)
Week 25			
n	18	17	16
Adjusted mean change (SE)	-62 (1290)	-3268 (1273)	-4093 (1390)
Adjusted mean difference vs. placebo		-3206	-4031
95% CI		(-6779, 366)	(-7844, -218)
p-value		0.08	0.04
Week 49			
n	18	18	14
Adjusted mean change (SE)	-2115 (1210)	-3851 (1169)	-4056 (1361)
Adjusted mean difference vs. placebo		-1736	-1941
95% CI		(-5090, 1618)	(-5601.86, 1720.15)
p-value		0.30	0.29

Source: page 88; check log transformed data

Figure 6 MMRM Analysis of change from baseline of serum creatine kinsase (IU/L)

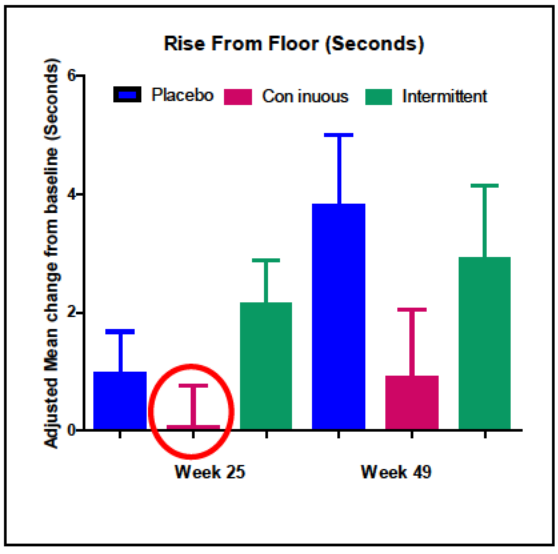


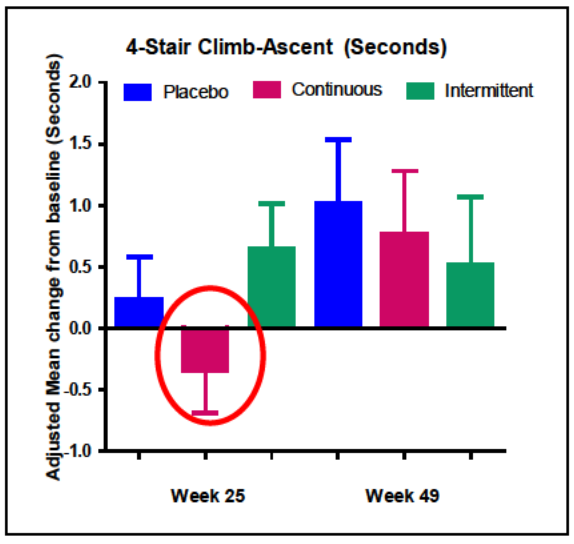
Reviewer's Assessment of Secondary Endpoints:

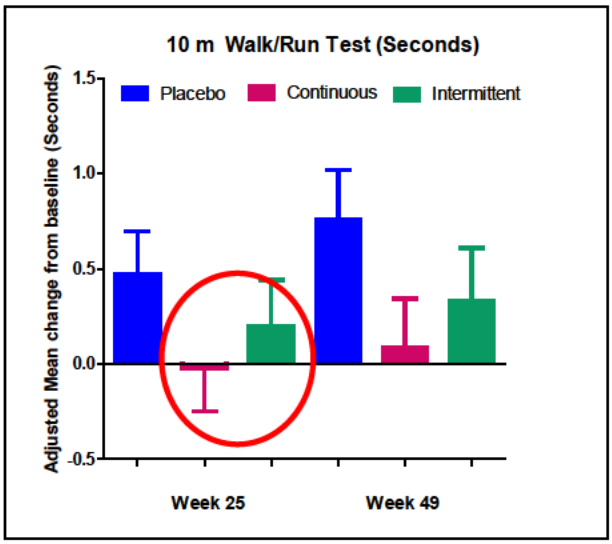
The secondary endpoints were not analyzed in a hierarchical manner and no endpoint was assigned as key endpoint, therefore the interpretation of these multiple endpoints is difficult.

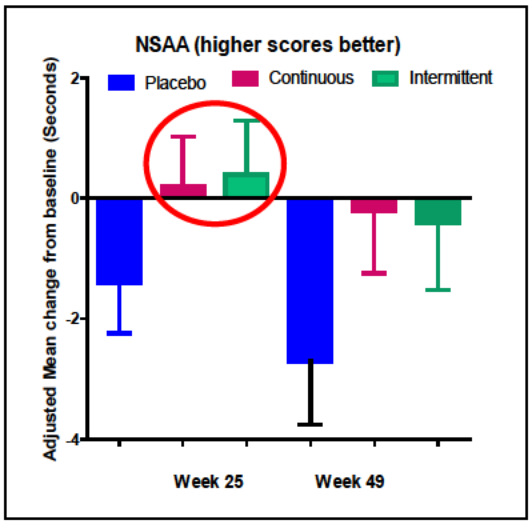
Timed Function Tests: The adjusted mean changes from baseline for the Timed Function tests and NSAA are graphically presented in Figure 7. NSAA scores stay stable for the 48 weeks for the continuous arm, but NSAA is shown to be stable in patients below the age of 7 years in the first year [+0.15 (SD 4.8)] (Mazzone 2013) and the continuous arm had higher percentage of subjects <7 years. All endpoints show a trend of improvement with the continuous regimen at Week 25 as shown by the circled data, which worsens at week 49, but remains better than placebo.

Figure 7 MMRM analysis of secondary endpoints at Week 25 and 49









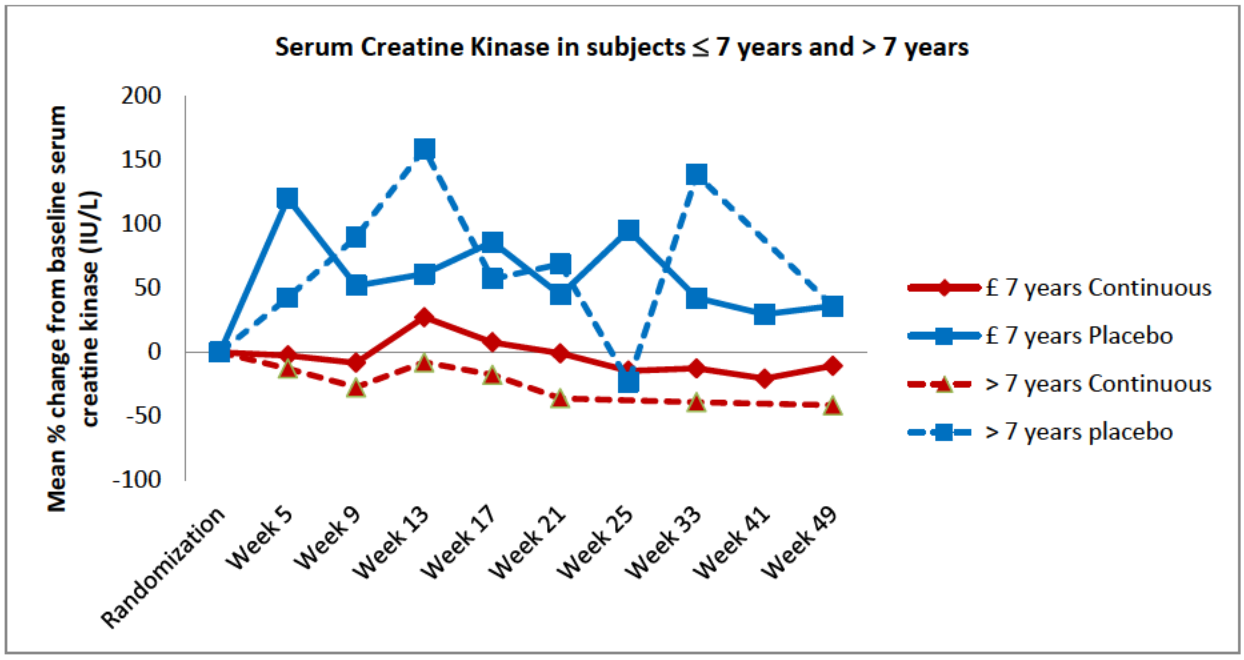
All Timed Function scores had 6 gradings (with 1 being unable to do the task and 6 easily do the task with least maneuvers). Very few subjects showed improvement in the grading scores (n ≤3) for Timed Function Tests, with the exception of 4-stair climb descent where 6 subjects showed improvement in the continuous group (e.g. holding one handrail vs. two handrails) compared to 2-3 subjects in the placebo and intermittent groups.

<u>Peds QL:</u> Parents perception of the problem was greater than that of the child's (e.g. More parent felt that their Child's leg hurts, child feels tired, child's back is stiff, wakes up tired etc.) at baseline. There was no systematic trend in the change from baseline at different visits. Many items on the PedQL neuromuscular module related to upper extremity weakness that are not likely to be impacted in an early ambulatory population (such as, My hands are weak, Hard to use my hands, long time to eat, hard to breath) and hence insensitive to overall meaningful change.

<u>Creatine Kinase:</u> Both drisapersen treatment arms showed a decline in CK compared to placebo, suggesting improvement in muscle cell integrity. However, this finding is associated with several confounders: CK levels are remarkably variable, with large within patient and between patient variability and are known to fluctuate day to day. It is affected by diurnal variation (increase during the day and decrease at night), exercise (reduced with inactivity), steroid use, and age (reduced with advancing age of the DMD boys as the muscle fibers are replaced with fat and fibrous tissue). There is no evidence of inactivity of the subjects from the Patient or Parent Reported Outcome measures, but the day to day activity level is unknown. The pain and discomfort from the injection site reactions could plausibly make the subjects less active.

Since CK peaks at ages 3-5 years and declines with age with levels reduced to 50% by age 7 years, I looked at the mean percent reduction of CK based on age. The following Figure shows the percent reduction in CK with treatment compared to placebo in subjects, ≤ 7 years and > 7 years. It is interesting to note that in this study Subjects >7 years had larger mean reduction in CK (-41%)

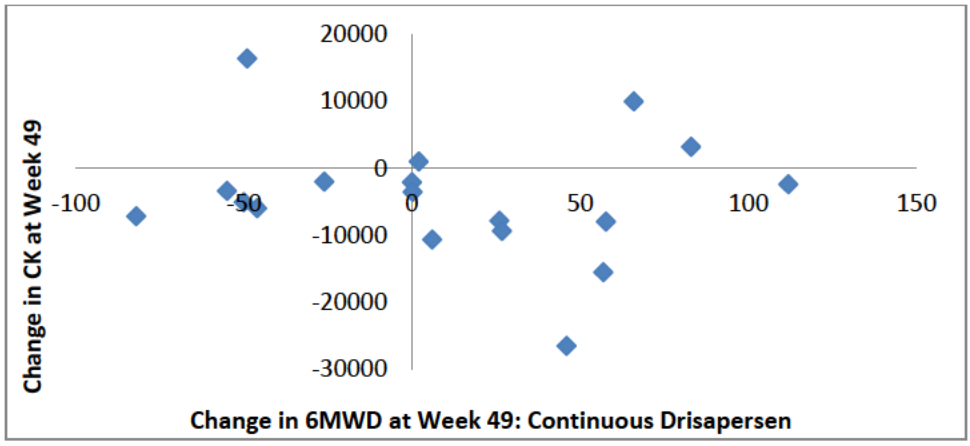
compared to subjects ≤ 7 years (-11%). This is consistent with a sub-group post-hoc analysis conducted by the applicant showing larger treatment benefit in older subjects. Given the small number of subjects and the large variability in the CK levels, this could be a chance finding and unreliable being post-hoc in nature. As a result of these confounding factors, a true treatment effect of a reduction in CK is difficult to discern.

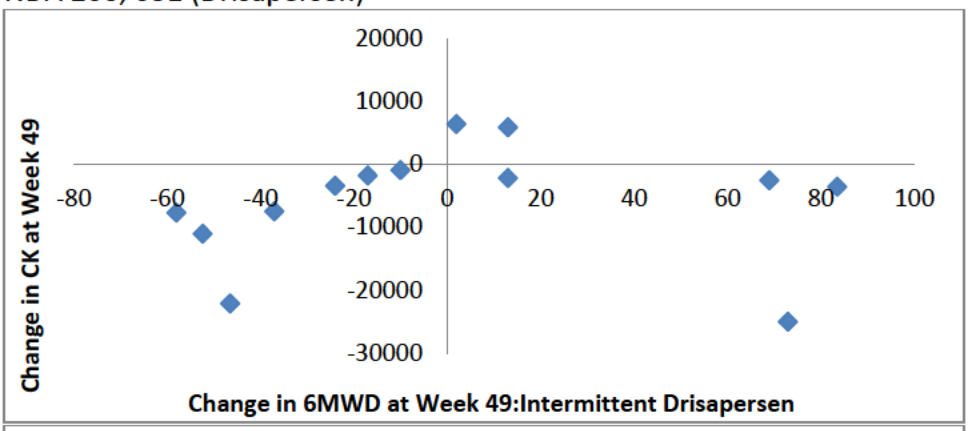


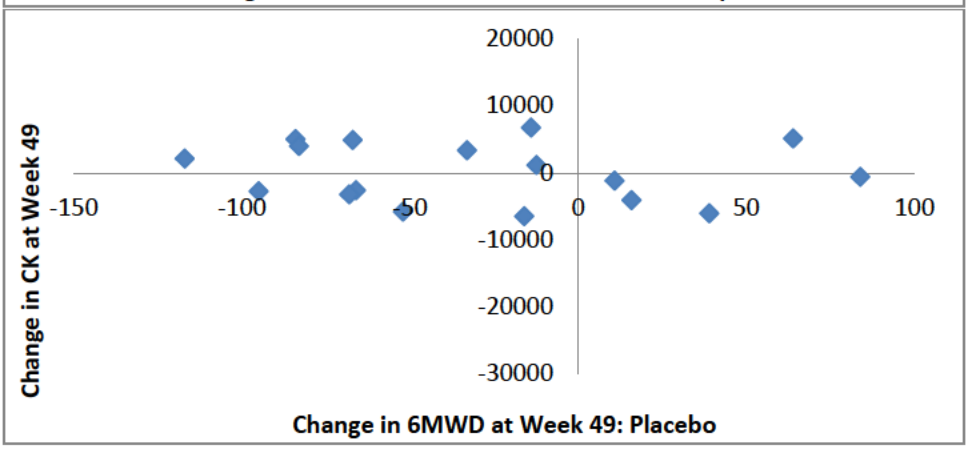
Note: Standard Deviations are not plotted as the variability is very high and overlaps between groups, including error bars constricts the graphs considerably

The following figures show the relationship of change in 6MWD and change in CK at Week 49.

- **No clear relationship between change in 6MWD and CK was observed at Week 49. The sample size of this study and the variability in the endpoints may preclude the ability to see any relationship in this study.**
- **There were a higher number of subjects showing a decline in CK in the drisapersen arm compared to the placebo arm.**







Dystrophin Measurements

Muscle biopsies from the tibialis anterior (TA) were obtained from most subjects and from the quadriceps of 5 subjects at baseline and at Week 25 and were analyzed using the following methods:

- Detection of exon 51 skipped mRNA by Reverse Transcription-Polymerase Chain Reaction (RT-PCR)
- Detection of dystrophin protein expression by:
  - Qualitative Western blot analysis (WB).
  - Qualitative immunofluorescence assay (IFA), including percent change from baseline.

Dystrophin exon 51 skipped-mRNA measured by RT-PCR

Exon 51 skipped mRNA was detected in 2/18 (12%) of subjects in the continuous group and 5/17 (29%) of subjects in the intermittent group compared to 0/18 subjects in the placebo group at week 25, as shown by increased intensity. Increase in exon skip was detected more in quadriceps biopsy (3/4, 75%) compared to TA muscle biopsy (4/30, 13%). An increase in Exon 51 skip intensity was defined as: skip copies/ non skipped copies (Post treatment –pre-treatment/pre-treatment)*100>1%

OBP Reviewer Dr. Rao's Comment on methodology:

The gel-based PCR method used by the applicant was not quantitative because it involved a visual assessment of whether or not a band for the skipped mRNA product was observed. In addition to treated samples, baseline samples also showed exon 51 skipped band in 100% of

patients. See Appendix B for additional comments on the impact of revertants on the PCR data and the limitations of measuring dystrophin mRNA.

With nested RT-PCR there was no apparent increase in median PCR fragment intensity at week 25 when comparing to pre-treatment biopsies for the drisapersen continuous group (Table 13). The applicant attributes this variable finding to the low number of subjects. There is also large variability in the samples in each group that obscures any conclusion of increase in dystrophin.

Table 13 Intensity of exon 51 skipped dystrophin mRNA product by nested RT-PCR

	Exon Skip (a.u) Mean (SD)	
Study Treatment	Week 0	Week 25
Placebo	1.30 (1.01)	0.73 (0.41)
Weekly 6mg/kg	1.29 (2.42)	1.30 (1.50)
Intermittent 6mg/kg	1.72 (2.38)	2.60 (1.29)

OBP Reviewer Dr. Rao's Comment on methodology:

The nested PCR approach used should provide the applicant greater specificity for detecting their exon skipped product because a second set of primers and PCR run were used to amplify a narrower region of the same target mRNA. However, this method does not provide absolute quantitation because no reference standard was used to provide a calibration curve. The quantitation provided with arbitrary units is derived from the relative band density of other samples and does not necessarily reflect copy numbers of the skipped product. See Appendix B for additional comments and supporting references.

Dystrophin Protein by IFA:

With IFA, an increase in the mean dystrophin of the entire fiber population was observed in 9/15 (60%) subjects in the continuous group and 4/15 (54%) subjects in the intermittent group compared with only 1/17 (6%) subject in the placebo group. An increase in dystrophin was defined as an increase in mean membrane intensity of more than 4% at week 25 compared to pre-treatment biopsy.
The dystrophin intensity as measured by IFA is shown in Table 14. Mean percent change shows a 3% increase in dystrophin in the drisapersen continuous group compared to a 3% decrease in placebo. The Mean % change in the intermittent group was minimal.

Table 14 Dystrophin Intensity measurement by IFA (change from baseline at week 25)

	Muscle	Placebo (combined) (N=18)		6 mg/kg Drisapersen Continuous (N=18)		6 mg/kg Drisapersen Intermittent (N=17)	
		n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Non-Qualified Mean	Quadriceps	0	0	2	4.0 (6)	1	30.0 (0)*

Percentage Change (%)	Tibialis Anterior	17	-3 (5.3)	14	3.5 (6.9)	15	0.9 (8.6)
	All	17	-3.1 (5.3)	16	3.5 (6.7)	16	2.7 (11.0)
Non-Qualified Q90 Percentage Change (%)	Quadriceps	0	0	2	0.5 (6.4)	1	46.0 (0)
	Tibialis Anterior Muscle	17	-2.6 (7.1)	14	5.7 (10.0)	15	2.6 (10)
	All	17	-2.6 (7.1)	16	5.0 (9.6)	16	5.3 (14.3)

Q90 mean is the mean fiber membrane of the 10% brightest pixels in the membrane

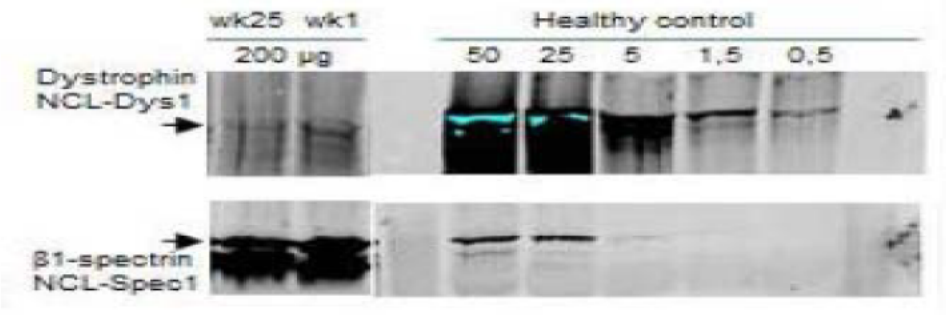
*Subject 2101 had the highest drisapersen concentration in the quadriceps (130 µg/g) and also the highest dystrophin

OBP Reviewer Dr. Rao's Comment on methodology:

No correlative human endpoint data (e.g. muscle function or dystrophin-associated protein complex (DAPC) protein co-localization) has been presented to support the biological/clinical significance of this scoring. See Appendix B for additional comments.

Dystrophin Protein by Western Blot:

With WB, an increase in the mean dystrophin intensity was observed in 5/17 (29%) subjects in the continuous group and 5/16 (31%) subjects in the intermittent group compared with 0/17 (0%) subject in the placebo group. An increase was defined as: (post treatment –pre-treatment/pre-treatment)*100>30%.



For western blotting, the applicant included serial dilution of a healthy control sample on each gel, although comparison between pre- and post-treatment samples from the same patient was used for scoring. No comparison was made to the values between the healthy controls dystrophin and the test samples.

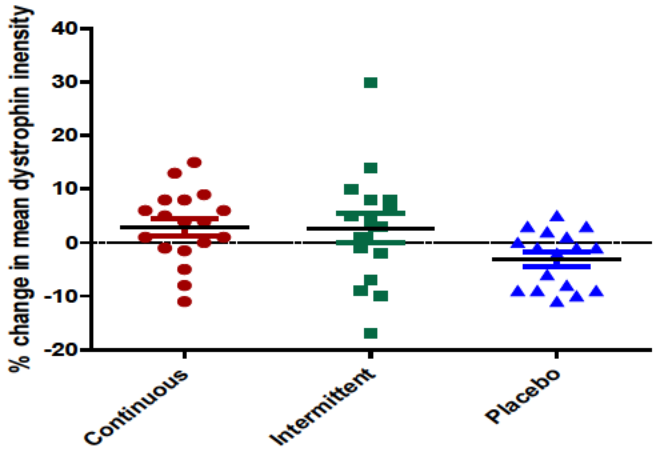
Reviewer's Assessment:

With WB, because baseline expression was at or below the lower limit of detection, the ratio of pre- to post-treatment expression in some cases was similar to "dividing by zero" leading to very high percent increases (up to 2500%) when the post-treatment expression level was only trace (about 1/3rd of 1% of normal levels). Some subjects similarly showed a large percent decrease in expression post-treatment likely due to small variations in measurements that were near zero.

In response to an FDA request about relative dystrophin in healthy tissue, the applicant provided data from five donor samples that show a range of 58-115% of the mean dystrophin value in quadriceps and 87-118% in tibialis anterior. Immunofluorescence results also showed similar variability and have been published by Beekman et al (2014). The applicant also states that the mean dystrophin intensity in the pre-treatment DMD biopsies can be estimated to be 0.3% of a particular control. In all but one post-treatment sample, the applicant estimates that the percentage of dystrophin detected was less than 1%, which they claim is the lower limit of detection for their assay.

The individual subject change in mean dystrophin intensity by IFA in the three groups is shown in Figure 8. There is a trend towards greater mean dystrophin intensity (by IFA) in the drisapersen treatment groups compared to placebo. There is an increase in dystrophin expression in higher number of subjects in the continuous drisapersen regimen. However, the small mean *increase* of 3-5% *from baseline* is unlikely to be biologically relevant.

Figure 8 % change in mean dystrophin intensity in individual subjects (IFA)



There was no clear relationship between the changes in dystrophin expression (as measured by IFA at Week 25) in the biopsy of the TA and the primary endpoint, the 6MWD at Week 25 or Week 49 (not shown).

A pharmacodynamic response was not detected in 30-40% treated patients. The applicant speculates that this could be related in part to: differences in characteristics of individual subjects (including but not limited to: stage and rate of disease progression; age; total weight; and muscle exposure on an mg/kg basis); treatment regimen, continuous vs. intermittent treatment (continuous showed a more consistent pharmacodynamic effect); and muscle group analyzed. TA muscle is relatively well preserved in the disease and therefore possibly less permeable to drug delivery and histological improvement difficult to detect in TA muscle. It is noteworthy that only 2 subjects in the continuous group and 2 subjects in the intermittent group showed an increase by all three methods. Dr. Rao's assessment of this overall conclusion is given below.

OBP Reviewer Dr. Rao's Comment:

A clear, consistent, and positive correlation between all three assays - IFA, WB, and Exon skip has not been established by the Applicant or published literature in the field using appropriate positive/negative controls (e.g. with BMD, DMD, healthy samples in the linear range). Taylor et al have reported a correlation between immunofluorescence-based intensity ratios of dystrophin/spectrin and dystrophin protein levels measured by Western blotting and normalized to actin. As presented by the applicant, the WB data is likely to be most reliable because a serial dilution with a healthy positive control was used for comparison and pre-treatment and post-treatment samples were run on the same gel in most instances. The IFA can suggest protein localization but is likely to be less meaningful for protein level quantitation. See Appendix B for additional comments on the caveats about each method.

Reviewer's overall assessment/discussion:

The strengths of Study DMD114117 are:

- **Primary endpoint (change from baseline 6MWD at Week 25) was positive for the continuous drisapersen treatment regimen with a treatment difference from placebo of 35 m (p=0.014) based on Applicant's pre-specified analysis.**
- **At Week 49 a similar *treatment difference* from placebo of 36 m was observed for the continuous drisapersen treatment regimen.**
- **Secondary endpoints measuring functions similar to walking [timed function tests (rise from floor, 10 m walk/run, and 4-stair climb/descent), and NSAA] also had directionally favorable trends for continuous treatment group at both Week 25 and 49, although not statistically significant. The secondary endpoints were not analyzed in a hierarchical manner, therefore the interpretation of these endpoints are difficult. Muscle strength did not favor drisapersen. Small changes in pulmonary function were similar across treatment groups.**
- **The percent reduction in serum creatinine kinase concentrations was 30-40% in the drisapersen treatment groups (p=0.08 and 0.04 at Week 25 for the continuous and intermittent regimen, respectively) compared to placebo.**

Some of the weaknesses of the study results are:

- **The intermittent drisapersen treatment group did not show a statistically significant treatment difference.**
    - **Both the continuous and the intermittent regimen have comparable total doses administered for the duration of the study.**
    - **Both regimens have identical plasma-concentration time profiles and should perform similarly (15% higher plasma AUC0-24 at Week 29 for the intermittent regimen).**
    - **The applicant states in the ISE that the difference between the intermittent and continuous treatment may have reflected the differences in age and advanced disease (time since diagnosis and duration of steroid treatment) in the intermittent group.**
        - **A post-hoc MMRM analysis with the two regimens combined showed a non-statistical difference from placebo of 20 m (p=0.12) at Week 25 and a treatment difference from placebo of 31 m (p=0.05) at Week 49. Given the**

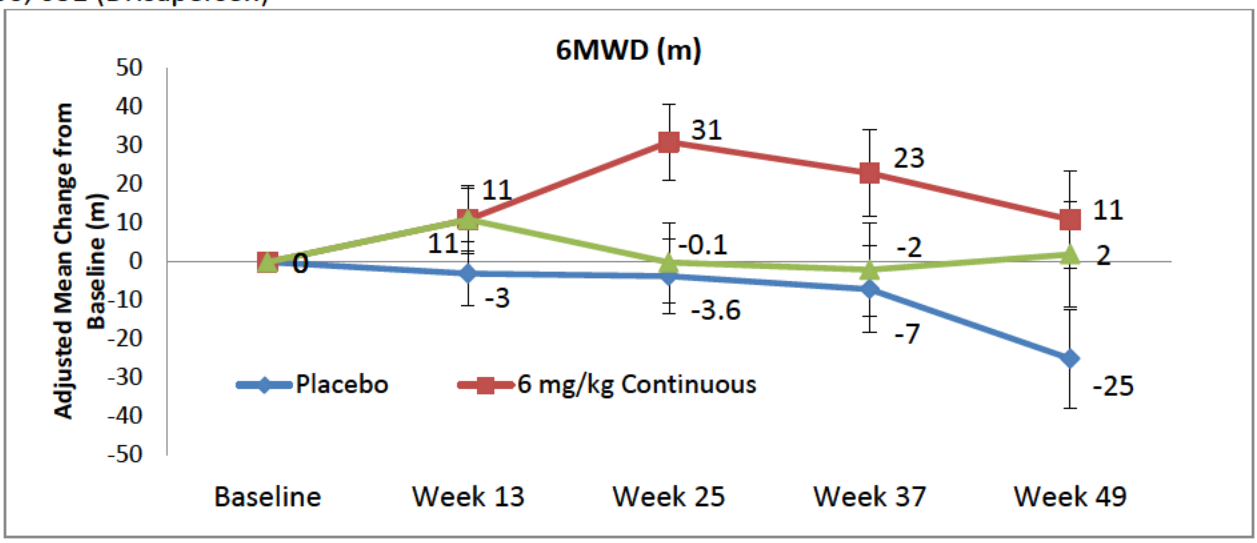
heterogeneity in the DMD population and in the study arms (as discussed below), a combining the two regimens suggest a treatment benefit with drisapersen at Week 49 and may be viewed as a strength of this study, even though post-hoc in nature.

- **Potential partial unblinding to the assigned treatment due to injection site reactions: Unblinding could affect the performance of 6MWD, which is considered an effort dependent endpoint. The incidence and the duration of injection site reactions was the largest for the 6 mg/kg continuous group and the least for placebo.**
- **Dystrophin expression increased *very slightly from baseline* in drisapersen treated subjects compared to placebo in some subjects**

Discussion on primary endpoint 6MWD:

- **The drisapersen continuous group appeared to consist of boys with less functional impairment compared to other treatment arms as discussed on page 37.**
- **The continuous group shows an initial increase in *change from baseline* 6MWD at Week 13 and 25 and declined in subsequent weeks.**
-
- Figure 9 **shows the magnitude of change from baseline at each time point. Improvement at Week 13 with both regimens could also be consistent with unblinding bias or the natural variation in the population. The change from baseline in the intermittent group on the other hand showed stability in the 48 weeks. The natural history studies also show that some subjects can remain stable in their ability to walk as assessed by 6MWD for 1-2 years before they begin to decline. It is uncertain if the improvement at Week 25 followed by decline is due to variability or a treatment effect.**
  The applicant includes in their discussion of the study: "It is not known whether the apparent increase and decline in 6MWD in the continuous regimen versus the relative stability in the intermittent regimen is due to the drug effect or simply a result of natural variation in the population. Longer term treatment data and data from a larger number of subjects are needed to determine such an effect (page 134 of study report)."

Figure 9 MMRM Analysis of change from baseline in 6MWD



- **The natural history data as published in the literature also show variation on the reported decline in 6MWD (-22 to - 58m per year based on literature). Given these concerns the benefit seen with the continuous drisapersen treatment group at week 25 may be a result of population variation (as shown in differences in disease characteristics at baseline), especially given that the intermittent regimen had a different treatment effect, as also speculated by the applicant. In DMD, fatigue and falls have been shown to be critical factors of six-minute walk distance variability. Motivation, concentration are other factors of variability for an effort dependent endpoint. The injection site reactions experienced by the subjects could add to the bias as well. Recent published data (Bello 2105) suggest that there are genetic modifiers that can either be associated with milder (LTBP4) of more progressive phenotypes (osteopontin gene-SPP1).**

<u>On secondary endpoints:</u>

- **The baseline imbalances in the continuous group would affect the secondary endpoints in a similar way.**
- **There was a greater decline in CK concentrations in the drisapersen intermittent treatment group compared to the continuous group, which is inconsistent with what was seen with 6MWD, NSAA, Rise From Floor, 10 m walk/run, nevertheless there was greater reduction in CK in drisapersen treated groups compared to placebo. There is a lot of variability in the assessment of CK that this may not be as concerning.**

6.2. Study DMD 114876

6.2.1. Study Design

Overview and Objective

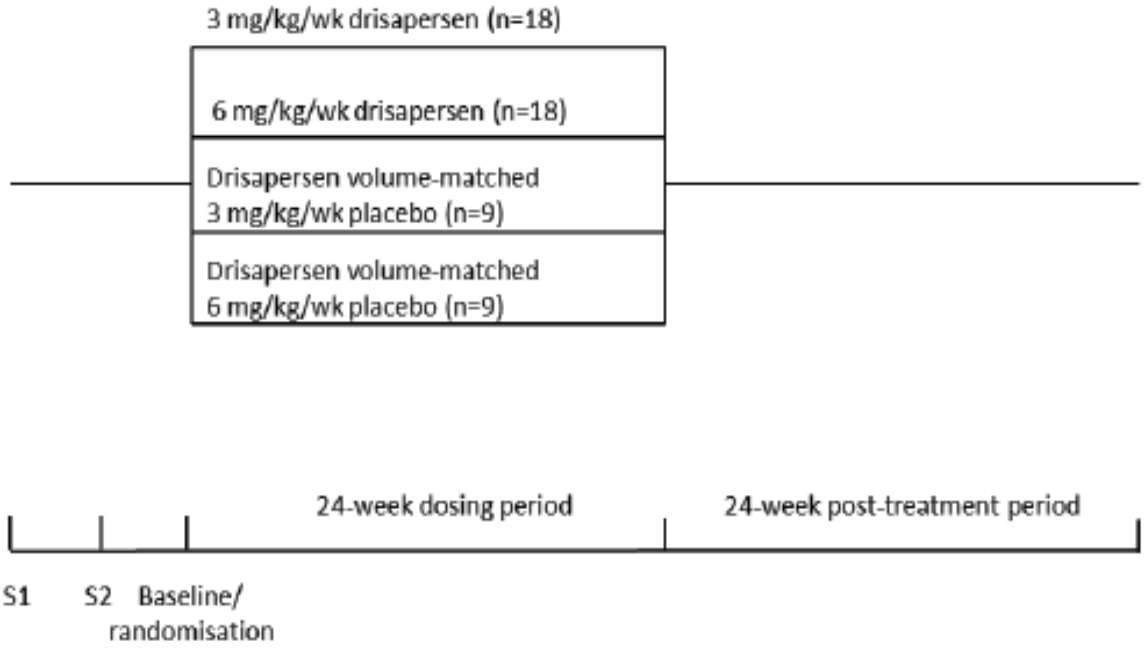
The primary objective of this study was to assess efficacy of 2 different doses of subcutaneous drisapersen versus placebo administered over 24 weeks in ambulant subjects with DMD. The

secondary objectives were to assess safety, tolerability, PK, dystrophin half-life and persistence of efficacy at 48 weeks.
Studied period**:** 26 Oct 2011-4 Nov 2103
Study center(s): 13 centers in the United States

Trial Design

The study design was similar to study DMD114117, with the exception of a treatment period of only 24 weeks: and included 2 doses. The study design schematic is given in Figure 10. Screen 1 and 2 were 4 and 2 weeks prior to randomization, respectively. After the last dose of drisapersen /placebo, subjects continued into a 24 week post-treatment period off drug, after which subjects had the option to enter an open label extension study with drug treatment or have a 20 week follow up if the patient did not enter the open label extension. There were no life style restrictions during the study.

Figure 10 Study design schematic for Study DMD114876



Population: N=54 ambulant DMD boys with a mutation corrected by exon 51 skipping. The sample size is not based on statistical considerations.
Key Inclusion Criteria: Same as Study DMD114117.
Amendment 3 of the protocol changed the rise time from floor to ≤15 seconds from ≤7 seconds (without aids/orthoses)
Key Exclusion Criteria: Same as Study DMD114117 with the addition of:

- Baseline platelet count below the Lower Limit of Normal
- aPPT above the Upper Limit of Normal
- History of significant medical disorder which may confound the interpretation of either efficacy or safety data e.g. inflammatory disease

Dosing Regimen:
Subjects were randomized to the following in 2:2:1:1 ratio using Interactive Voice Response System:

- 3 mg/kg/week SC drisapersen for 24 weeks (N=18)
- 6 mg/kg/week SC drisapersen for 24 weeks (N=18)
- 3 mg/kg/week SC placebo for 24 weeks (N=9)
- 6 mg/kg/week SC placebo for 24 weeks (N=9)

Injections were rotated on different sites in the abdomen, back, arm and thighs. Volume of placebo was matched to the dose to maintain the blind and limit bias. The different doses were not fully blinded, but administered by personnel not involved in efficacy assessments (Subjects on 3 mg received a lower volume of injection). Blinding of the study was maintained until completion of Week 24 assessment. After the 24 week analysis, the results were not communicated to the investigators or monitors.
The purpose of the post-treatment phase was to model the half-life of dystrophin, assess maintenance of response, and provided information about resolution of adverse event and laboratory abnormalities following cessation of treatment.

Study Endpoints

The following efficacy assessments were assessed at screening (1 and 2), randomization, week 24 or early withdrawal and week 48 or follow-up unless specified otherwise.
The primary efficacy endpoint were the same as Study DMD114117: 6MWD at week 24
6MWD
The secondary efficacy endpoints were also the same with the exception of the following additional secondary endpoints:

- The pulmonary function tests included (FEV_1, FVC, PCF, PF, sniff pressure test)
  (Study DMD114117 had MIP and MEP instead of sniff pressure test)
- Clinical global Impression of Improvement
  The CGI-I was measured on a 7-point Likert scale (1 = 'very much improved', 2 = 'much improved', 3 = 'minimally improved', 4 = 'no change', 5 = 'minimally worse', 6 = 'much worse', 7 = 'very much worse').
- Functional Outcome Assessments:
  - Physician Assessment of Daily Living [the ability of the subject to perform usual day-to-day activities (e.g., general health, mobility, general daily activities)]
  - Functional Outcomes Survey by Family/caregiver

Most secondary endpoints were not assessed at week 48, with the exception of CGI and Functional Outcomes Survey. Pediatric Quality of Life was not a secondary endpoint in this study.
Other:

- Dystrophin expression (muscle biopsies from tibialis anterior) was done at baseline, Week 24 in all subjects, and an randomly assigned third biopsy at Week 12 or Week 36 visit
- mRNA production in muscle tissue.
- Drisapersen in muscle tissue

Exploratory endpoints: at baseline, week 24 and 48

- A set of T1-weighted (T1w) images to assess the level of fat infiltration and quantified according to the Mercuri scale and apparent fat fraction and set of T2-weighted (T2w) images to assess the combined effects of fat infiltration and edema and quantified according to the normalized T2-weighted signal intensity and T2 relaxation rate in skeletal muscle in the thigh as determined by structural MRI measures over time (optional for subjects). MRI scans of the mid-thigh were performed.
- 6MWD at week 48

Statistical Analysis Plan

Efficacy parameters were analyzed using the ITT population (same definition as Study DMD114117).

Primary Endpoint Analyses: Primary assessment of efficacy data was conducted using MMRM at week 24 on the Observed case (OC) data. The analysis was similar to StudyDMD114117. Due to the two different doses, Type 1 error rate was preserved by utilizing a hierarchical approach, with 6 mg being assessed first. If no statistically significant difference was observed between the 6 mg/kg dose and placebo, then further analyses of the 3mg/kg dose were considered exploratory.
Sensitivity Analyses for primary endpoint: Same as Study DMD114117
Secondary endpoint analyses:

- For continuous endpoints ANCOVA analyses on OC data, with fixed terms of treatment center and baseline score (For Study DMD114117 MMRM analysis on OC data was used)
- Kaplan-Meir and Log rank test on time to event endpoints such as loss of ambulation

Protocol Amendments

Protocol amendments related to efficacy assessments are summarized below.

Amendment 1 ((09 Sep 2011)	No significant change that would affect efficacy assessments
Amendment 2 (27 April 2012)	Muscle Biopsies to be conducted after functional efficacy assessments, no more than seven days after the scheduled visit.
Amendment 3 (09 Aug 2012)	Able to rise from floor in ≤15 seconds (without aids/orthoses) at Screening Visit 1 and Screening Visit 2 instead of in ≤7 seconds (without aids/orthoses) in the original protocol. Sponsor's rationale: A review of blinded data from other ongoing Drisapersen studies suggests an increase to the RFF inclusion criteria to include subjects with RFF up to 15 seconds at screening should not increase the likelihood of subjects losing ambulation during the study or increase variability in the 6MWD significantly. It will enable more potential subjects in this rare disease to be eligible.

Reviewer's Comment: The impact of including subjects with rise from floor in ≤15 seconds will be discussed in the results section.

Management of clinical data was performed in accordance with GSK standards. The study was conducted in accordance with ICH GCP (ICH E3 and E6) and applicable country-specific requirements. Written commitments were obtained from investigators to comply with GCP. Study was conducted with written informed consent from subjects and their parents.

6.2.2. Study Results

Patient Disposition

All 51 subjects completed the study. The distribution of subjects in each group is given in Table 15.

Protocol Violations/Deviations

A total of 4 subjects had major protocol violations. (Table 15)

Table 15 Protocol Violations

	Number (%) of Subjects			
	Placebo (combined) (N=16)	Drisapersen 3 mg/kg/week (N=17)	Drisapersen 6 mg/kg/week (N=18)	Total (N=51)
Intent-to-Treat Population	16 (100)	17 (100)	18 (100)	51 (100)
Per Protocol Population	15 (94)	14 (82)	18 (100)	47 (92)
Total Number of Subjects with Major	1 (6)	3 (18)	0	4 (8)
Subject 000226 had history of aortic root dilatation	0	2 (12)	0	2 (4)
Subject 000176 had idebenone until Day 3	0	1 (6)	0	1 (2)
Subject 000176 missed 5 doses (<80% compliant)**	0	1 (6)	0	1 (2)
Subject 000201 with history of cardiomyopathy being managed with lisnopril	0	1 (6)	0	1 (2)
Subject 000158 Treatment blind broken*	1 (6)	0	0	1 (2)

*due to ER visit for flu-like symptoms (a member of the investigators staff was unblinded). The family stated the ER staff did not unblind them to the treatment assignment; however this could not be positively confirmed.
**protocol required follow-up for lab values falling outside the study reference ranges (proteinuria)

Reviewer's Comment: The Protocol deviations were all in the 3 mg/kg group, except one in the placebo group. The impact of this subject is shown in the Sensitivity analysis.

Table of Demographic Characteristics

Baseline demographic characteristics were similar across treatment groups with the drisapersen 6 mg/kg group having slightly lower median age (Table 16).

Table 16 Summary of demographic characteristics

	Number (%) of Subjects			
	Placebo (combined) (N=16)	Drisapersen 3 mg/kg/week (N=17)	Drisapersen 6 mg/kg/week (N=18)	Total (N=51)
Age (yrs)				
Mean	8.0	7.8	7.6	7.8
SD	1.79	1.91	2.70	2.15
Median	8.0	8.0	6.5	8.0
Min., Max.	5, 11	5, 11	5, 13	5,13
Ethnicity				
Hispanic/Latino	4 (25)	1 (6)	1 (6)	6 (12)
Not Hispanic/Latino	12 (75)	16 (94)	17 (94)	45 (88)
Race				
African American/African Heritage	1 (6)	1(6)	1(6)	3 (6)
Asian – East Asian Heritage	0	0	1 (6)	1 (2)
Asian – South East Asian Heritage	0	0	1 (6)	1 (2)
White – White/Caucasian/European Heritage	14 (88)	16 (94)	15 (83)	45 (88)
Mixed Race	1 (6)	0	0	1 (2)
Height (cm)				
Mean (SD)	123 (6)	120(8)	120 (14)	NA
Median	122	120	117	NA
Min., Max.	109, 133	102, 130	101, 146	NA
Weight (kg)				
Mean (SD)	30 (9)	29 (6)	30 (13)	NA
Median	28	31	25	NA
Min., Max.	19, 51	18, 42	17, 64	NA

Source: Study report DMD114876, page 69

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Other baseline characteristics are summarized in Table 17. There were some differences in corticosteroid use and duration across treatment groups. The subjects in the 6 mg/kg group had the shortest time since first symptoms.

Table 17 Summary of disease characteristics

	Number (%) of Subjects			
	Placebo (combined) (N=16)	Drisapersen 3 mg/kg (N=17)	Drisapersen 6 mg/kg (N=18)	Total (N=51)
Time Since First Symptoms (months)[a]				
Mean (SD)	57 (30)	67 (27)	59 (30)	61 (29)
Median	60	60	60	60
Min., Max	13, 112	25, 124	8, 112	8, 124
Time Since Diagnosis (months)[a]				
Mean (SD)	46 (30)	47 (26)	46 (27)	46.4 (27)
Median	45	38	46	43
Min., Max.	9, 111	13, 108	7, 96	7, 111
Time Since First Corticosteroid Taken (months)[a]				
Mean (SD)	37 (24)	33 (16)	27 (22.51)	32 (21)
Median	39	28	19	27
Min., Max.	7, 85	8, 58	6, 81	6, 85
Corticosteroid Regimen[b]				
Continuous	15 (94)	15 (88)	18 (100)	48 (94)
Intermittent	1 (6)	2 (12)	0	3 (6)
6MWD (m)				
Mean	416	415	396	NA
(SD)	(57)	(58)	(61)	NA
EXON Mutation, n (%)				
DMD 43-50 deletion	0	0	1 (6)	1 (2)
DMD 45-50 deletion	9 (56)	4 (24)	4 (22)	17 (33)
DMD 47-50 deletion	1 (6)	0	0	1 (2)
DMD 48-50 deletion	4 (25)	5 (29)	3 (17)	12 (24)
DMD 49-50 deletion	1 (6)	5 (29)	6 (33)	12 (24)
DMD 50 deletion	1 (6)	2 (12)	1 (6)	4 (8)
DMD 52 deletion	0	1 (6)	3 (17)	4 (8)

Source: Study report DMD11487, page 70

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Concomitant medication usage was similar across groups. Fifty subjects (98%) were >80% compliant. Duration of exposure was similar across groups.

Reviewer's Assessment of Baseline characteristics:

The baseline assessment of functional capabilities in each treatment group is summarized below:

Baseline Factors	Continuous 6mg/kg/week	Continuous 3 mg/kg/week	Placebo
Age <7 years	50%	24%	25%
6MWD>400m	44%	52%	75%
Rise From Floor <4 secs	28%	35%	50%
On continuous regimen	100%	88%	94%
Other factors: Ability to jump with both feet up at the same time	61%	82%	81%
Ability to hop with clearing foot and heel from floor	38%	58%	56%
Ability to rise from floor without gower's maneuver	0%	0%	13%

A higher percentage of subjects were of age <7 years in the 6 mg/kg/week group that tend to improve in function. The 3 mg/kg/week group has some factors that could suggest lower functional capability compared to the placebo group, such as percent of subjects with Rise from Floor<4s and 6MWD>400m.

Efficacy Results - Primary Endpoint

Applicant's analysis:

In the primary efficacy MMRM analysis of change from baseline in 6MWD (m) at Week 24, a non-statistically significant (p=0.07) difference of 27 m was observed for the 6mg/kg group compared to placebo. The difference observed at 24 weeks was maintained at 48 weeks (28 m) during the drug free period and so was the change from baseline 6MWD. A decrease of baseline of 11-13 m was observed at week 24 and 48 in the placebo group. The applicant considers this modest decrease consistent with the range expected in an early ambulant population (Table 18).

Table 18 Summary of Repeated Measures Analysis of Change from Baseline in 6MWD (m) by Visit

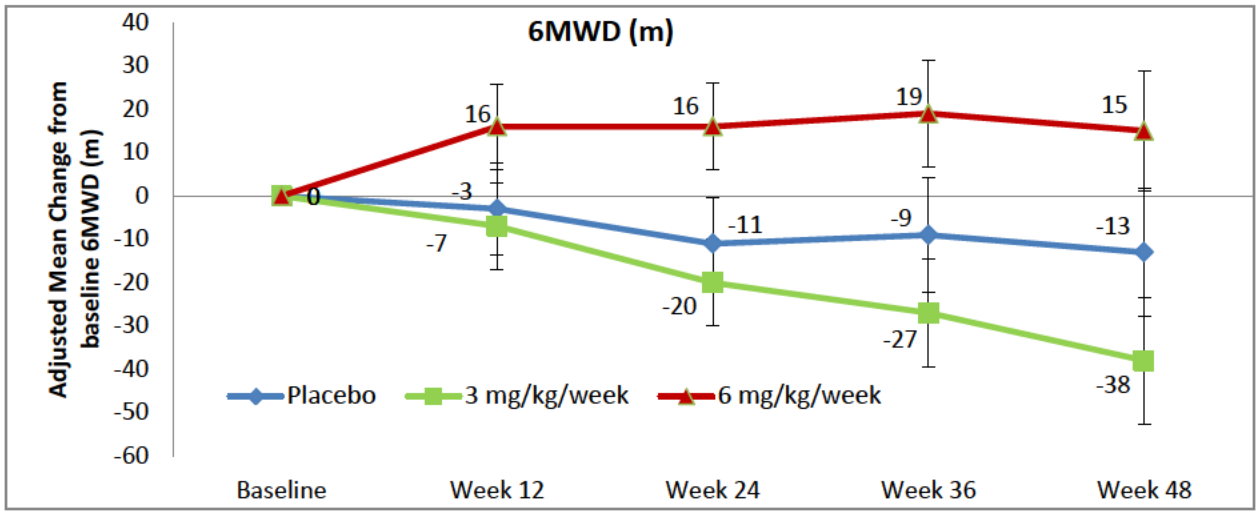
	Placebo (combined) (N=16)	Drisapersen 3 mg/kg/week (N=17)	Drisapersen 6 mg/kg/week (N=18)
Baseline			
n	16	17	18
Mean (SD)	416 (57)	415 (58)	396 (61)
Week 24 primary analysis			
n	16	17	18
Adjusted mean change (SE)	-11(11)	-20 (10)	16 (10)
Adjusted mean difference vs. placebo		-9	27
95% CI		(-39, 21)	(-2, 56)
p-value		0.55	0.07

Week 48 (end of post treatment period)			
n	15	17	18
Adjusted mean change (SE)	-13 (15)	-38 (14)	15 (14)
Adjusted mean difference vs. placebo		-25	28
95% CI		(-66, 17)	(-13, 69)
p-value		0.24	0.18

Source: DMD114876 study report, Page 74

None of covariates (visit, treatment, center grouping, baseline 6MWD, age, and age group) tested were significant at the 5% or 10% level.

Figure 11 MMRM analysis of change from baseline at week 24 and 48



Applicant's Sensitivity Analysis:

Sensitivity analyses with the ITT population show similar magnitude of treatment difference. A lower magnitude of treatment difference was observed with the PP population after removing the protocol violators.

Drisapersen 6 mg/kg/week Sensitivity Analyses: Change from Baseline in 6MWD (m) at Week 24

Analysis	Population	Dataset	Treatment Difference	95% CI	P-value
Drisapersen 6 mg/kg/wk					
MMRM	ITT	OC	27	(-2, 56)	0.07
MMRM	PP	OC	19	(-11, 50)	0.21
ANCOVA	ITT	OC	27	(-3, 57)	0.07
ANCOVA	ITT	LOCF	27	(-3, 57)	0.07

Source: DMD114876 study report, page 76

Reviewer's Comment: One subject in the placebo group made this difference. The subject # 158 in the placebo group had a 6MWD decline of 70 m and had the second largest decline in the placebo group (-127m was the largest decline at Week 24). This subject had his treatment unblinded due to an ER visit.

Additional Analyses on 6MWD:

1. Change from baseline in 6MWD by response category
   Response was measured as the percentage of subjects that achieved a fixed change in 6MWD (≥-10%, ≥0%, ≥10%, ≥20% and≥30% change). Subjects could be included in more than 1 category. At week 24, 3 subjects showed ≥10% change in the 6 mg/kg/week group and none in the placebo. At 48 weeks 8 subjects showed ≥10% change in the 6 mg/kg/week group and one in the placebo group. 8 subjects in the 6 mg/kg/week group and 2 subjects in the placebo group had ≥30 m change in 6MWD.
2. Change from baseline in percent-predicted 6MWD
   As 6MWD distance is influenced by age and development, analysis of the percent-predicted 6MWD that takes these factors into account were conducted (Henricson 2012). A treatment benefit (~5% difference) in favor of the 6 mg/kg group over placebo was observed at Week 24 (p=0.05). A treatment difference of -1.5% was observed with the 3mg/kg group at Week 24.
3. Number of Falls: Number of falls were similar across treatment groups
4. Loss of ambulation: No subject in any group lost ambulation during the study.

Post-hoc analyses on 6MWD:

By age group (≤7 and > 7 years): No statistically significant treatment differences were noted for either drisapersen treatment group compared to placebo, but the mean treatment difference from placebo was 31m in subjects ≤ 7years.

Table 19 Summary of Repeated Measures Analysis of Change from Baseline in 6MWD by Visit Split by Age Group

	Placebo (combined) (N=16)	Drisapersen 3 mg/kg (N=17)	Drisapersen 6 mg/kg (N=18)
≤ 7 years at baseline			
Baseline			
n	6	8	10
Mean (SD)	445 (63)	439 (50)	385 (60)
Week 24			
n	6	8	10
Adjusted mean change (SE)	-14 (21)	-22(18)	17 (17)
Adjusted mean difference vs. placebo		-8	31
95% CI		(-66, 49)	(-29, 90)
p-value		0.77	0.29
>7 years at baseline			
Baseline			
n	10	9	8
Mean (SD)	399 (48)	394 (59)	410 (62)
Week 24			
n	10	9	8
Adjusted mean change (SE)	-16 (12)	-16 (12)	12 (14)
Adjusted mean difference vs. placebo	NA	-0.14	28
95% CI	NA	(-39, 39)	(-9, 65)
p-value	NA	0.99	0.13

Source: DMD114876 study report, page 82

Reviewer's Comment:

- **This post-hoc analysis is un-interpretable due to small number of subjects. It is noteworthy, that Study DMD114117 showed larger treatment difference in subjects >7 years.**
- **In this study the impact of including subjects with Rise from Floor of ≤15 seconds was not significant as only two subjects were enrolled with RT of >7 seconds (one in the 3 mg/kg group with RT of 10 seconds and one in the 6 mg/kg group with RT of 12 seconds.**

Data Quality and Integrity - Reviewers' Assessment

There are no data integrity issues.

Dose/Dose Response

There was no clear dose-response established. It is unclear why the 3 mg/kg performed worse than placebo and may suggest random noise.

Efficacy Results - Secondary and other relevant endpoints

Applicant's Analysis:

Timed Function tests, NSAA, Muscle Strength, and Pulmonary Function:
At Week 24, changes on timed function tests (rise from floor, 10 m walk/run, 4-stair climb) were small (generally less than one second). Rise from floor, 4-stair climb, muscle strength and NSAA favored the 3mg/kg group more (Table 20). The number of subjects improving or worsening was similar for each test or showed greater number of subjects worsening from baseline in the Rise from floor and 10 m walk/run in the 6 mg/kg group. Changes in pulmonary function measures were small and variable across both treatment groups. The secondary endpoints were not measured in the post treatment period at Week 48.

Table 20 Secondary Endpoints, unadjusted mean baseline (SD), adjusted treatment difference (95% CI), p-value at Week 24

	Placebo (n=16)	3mg/kg/week (n=17)		6 mg/kg/week (n=18)	
Rise from Floor (s)					
Baseline (SD) Adj. treatment difference	4.49 (1.61)	4.96 (2.21) 0.39	p=0.69	5.19(2.46) 0.83	p=0.38
10 m walk/run (s)					
Baseline (SD) Adj. treatment difference	5.12 (1.35)	4.97 (1.17) 0.56	p=0.05	5.38 (1.35) 0.04	p=0.89
4 step ascent (s)					
Baseline (SD) Adj. treatment difference	3.53 (1.80)	3.14 (1.29) 0.002	p=0.99	4.60 (3.17) -0.80	p=0.06
4 step descent (s)					

Baseline (SD) Adj. treatment difference	2.94 (1.2)	3.34 (2.2) -0.68	p=0.31	4.05 (2.3) -0.41	p=0.52
NSAA (total score)					
Baseline (SD) Adj. treatment difference	26.5 (5.0)	26.5 (5.2) -0.49	p=0.68	24.6 (5.7) -0.18	p=0.87
Muscle Strength					
Baseline (SD) Adj. treatment difference	128.4	129.2 (22) 2.36	p=0.72	125.2 (43) 0.82	p=0.89

Source: Adapted from applicant's analysis.

Creatine Kinase:

A decline in CK was observed from baseline at Week 24 for both active treatment arms compared to placebo, with a greater treatment difference for the drisapersen 6 mg/kg/week group than for the drisapersen 3 mg/kg/week group. However at the end of the post-treatment period at week 48, a continued decrease in CK compared with placebo was observed for the drisapersen 3 mg/kg/week arm, but not for the drisapersen 6 mg/kg/week arm (Table 21).

Table 21 **Summary of Repeated Measures Analysis of Change from Baseline in Creatine Kinase Serum Concentration (IU/L) by Visit**

	Placebo (combined) (N=16)	Drisapersen 3 mg/kg (N=17)	Drisapersen 6 mg/kg (N=18)
Baseline			
n	16	15	18
Mean (SD)	12715 (5606)	14553 (7810)	13059 (8288)
Week 24			
n	16	17	17
Adjusted mean change (SE)	-3479 (1230)	-4079 (1173)	-4537 (1189)
Adjusted mean difference vs. placebo	NA	-600	-1058
95% CI	NA	(-4121, 2920)	(-4456, 2340)
p-value	NA	0.73	0.53
Week 48			
n	15	17	18
Adjusted mean change (SE)	-2783 (1249)	-4838 (1171)	-2616 (1149)
Adjusted mean difference vs. placebo	NA	-2055	167
95% CI	NA	(-5587, 1478)	(-3209, 3544)
p-value	NA	0.25	0.92

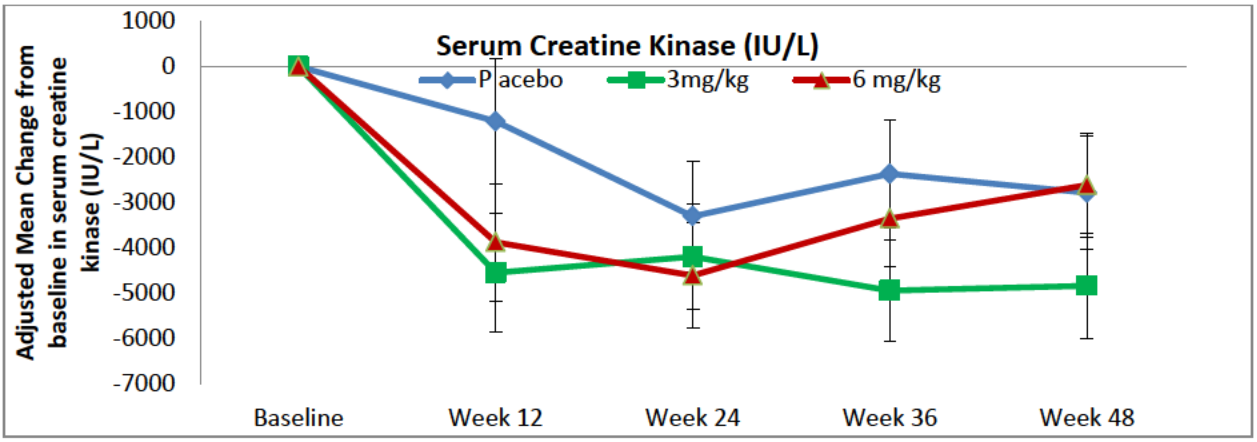
Source: DMD114876 Study Report, page 96

Reviewer's Comment:

The 3 mg/kg dose group continues decline during the drug free period up to Week 48, but the 6 mg/kg dose group shows an increase in CK. The reliability of this finding is unclear. Exercise induced changes in CK are difficult to ascertain, nevertheless CK declined in drisapersen treated groups.

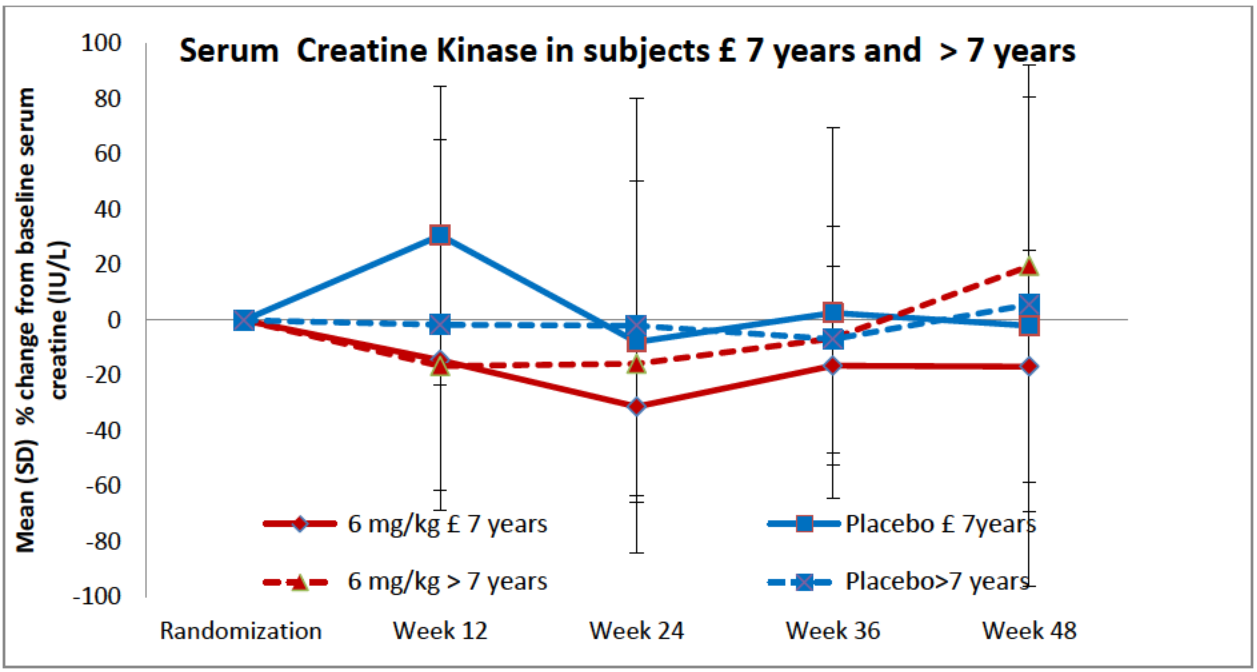
Clinical Review (Efficacy)
NDA 206, 031 (Drisapersen)
Figure 12 shows the time course of adjusted mean change in CK.

Figure 12: MMRM analysis of change from baseline in serum creatine kinase concentrations



In a post-hoc subgroup analysis, subjects ≤7 years showed greater treatment difference on 6MWD compared to subjects >7 years, therefore I looked at percent reduction of CK in these subgroups. Consistent with the finding with 6MWD, the reduction in CK was greater in subjects ≤7 years compared to subjects >7 years (Figure 13). The sample size is small and variability is large, therefore these findings should be interpreted with caution.

Figure 13 Change from baseline serum creatine kinase in subjects ages ≤7 years and > 7 years



CGI, Functional Outcome Survey, Physician assessment of daily living:

No differences among treatment groups were observed on CGI-I and Functional Outcome Survey (29 assessed by parents (including general health, mobility, physical activities, hand dexterity and use of assistive devices domains). For CGI-I, there were 11% (2/18) with "much improved" or "very much improved" response in the 6 mg/kg group and 14% (2/14 responders in the placebo group. For the Functional outcome survey, some trends in favor of the 6 mg/kg group were observed for "general health" and "hand dexterity" compared to placebo and 3 mg/kg group. On some questions in the functional outcome survey, placebo and 3 mg/kg were rated as "improvement".

MRI:

The applicant cites MRI data showing trends for reduction in edema (swelling) and adipose (fatty tissue) replacement signals at Week 24 and Week 48, based on T2 mapping and fat fraction methodology, in the small number of subjects. The applicant concludes:

- T2-weighted signal decreased (-0.07 to -0.23; N = 14) compared to controls (0.07 – 0.14; N = 10)
- Apparent fat fraction increased (2.7 – 5.2%; N = 5) in placebo group compared to 6 mg/kg/week treatment (0.9 – 3.8%; N = 6), suggesting a reduced rate of fat infiltration in subjects in 6 mg/kg.
- Effects persisted up to 24 weeks post-treatment

Consult review of the MRI data conducted by Dr. Daniel Krainak (CDRH Imaging Division) concludes that the data presented in the application are unconvincing for several reasons: the small number of subjects with fat fraction data at baseline, 24 weeks and 48 weeks, variability in the MR systems used, and lack of data concerning the actual quality control measurements from phantoms. The limited data show substantial overlap between treatment groups, large variability by muscle and a wide range of fat fraction observed at baseline. The magnitude of the changes observed in the study population is on the order of the uncertainty in the measurement technique (approximately 3%). Dr. Krainak concludes greater uncertainty about quantitative T2 measures in the context of edema as T2 may be influenced by many physiologic factors (including inflammation/edema, local bleeding/hematocrit, fat, [fat effects T1 more than T2] and more). Most of the commonly seen pathologies (infection/inflammation, tumor [benign or malignant], etc.) lead to an increase in T2 values. Therefore, an altered T2 is sensitive but not specific unless correctly interpreted in the context of the underlying pathophysiology.

Dystrophin Measurements

Muscle biopsies were obtained from the tibialis anterior (TA) muscle from each subject at baseline, Week 24 and either week 12 or 36. The following analyses were done:

- Detection of exon 51 skipped mRNA by RT-PCR
- Detection of dystrophin protein expression at baseline and Weak 24 (N=36) and at Week 12 by IFA (N=4)
- Detection of dystrophin protein expression at baseline and Week 24 (N=9) by WB analysis, when IFA was not possible because of poor sample quality for IFA. For 2 subjects WB analysis was performed to confirm IFA results.

Exon 51 skipped mRNA by RT-PCR

A total of 10/17 (59%) subjects in each of the drisapersen 3 mg/kg/week group and 6 mg/kg/week group compared to 2/15 (13%) subjects in the placebo group had an increase in exon 51 skipping

compared to baseline (Table 22). For about 24-60% of the subjects, the relative intensity was below the reporting level across treatment groups. The applicant notes that the increase was more pronounced at week 36, where 43% of the 3 mg/kg and 100% of the 6 mg/kg subjects and 14% in the placebo group showed an increase in exon skipping (Note: sample size, N=7 at week 36). Note that doses were administered only up to 24 weeks.

Table 22 Summary of DMD Exon 51 Skip Muscle Biopsy Data at Weeks 12, 24, and 36

Parameter/ Visit	Result	Number (%) of Subjects		
		Placebo (combined) (N=16)	Drisapersen 3 mg/kg (N=17)	Drisapersen 6 mg/kg (N=18)
Relative Intensity				
Week 12	n Increase	7 1 (14)	6 3(50)	8 4 (50)
Week 24	n Increase	15 2 (13)	17 10 (59)	17 10 (59)
Week 36	n Increase	7 1 (14)	7 3 (43)	7 7 (100)

Source: adapted from Page 98

The mean PCR fragment intensity (a.u) for exon 51 skipped product was increased for both 3 and 6 mg/kg at Week 24 (**Table 23**).

Table 23 Intensity of exon 51 skipped dystrophin mRNA product by nested RT-PCR and capillary electrophoreses

Study Treatment	Exon Skip (a.u) Mean (SD)	
	Week 0	Week 25
Placebo	2.0 (1.5)	1.5 (1.2)
Weekly 3mg/kg	2.7 (4.1)	4.4 (3.6)
Weekly 6mg/kg	2.4 (4.4)	4.4 (6.6)

The applicant also provided Digital Doppler PCR (ddPCR) data with supporting information that the assay precision was >25% and the limit of reporting for DMD biopsies carrying exon 50 deletion was >140 for skipped copy numbers in total 1500 ng RNA. The RNA integrity number (RIN) value for many samples was lower than 5, suggesting moderate to low RNA quality (the highest possible value being 10). The applicant has provided ddPCR data for all RIN value samples and those with RIN >5. No appreciable increase in skip numbers relative to placebo group was observed in majority of the samples of the treated groups.

OBP Reviewer Dr. Rao's Comment on Methodology:

Given that the applicant identified a high inter-assay variation of 25%, it is unlikely that this method, as performed, could provide the Applicant with any meaningful quantitative data regarding dystrophin mRNA because the relative increases in mRNA are small and in most instances within the applicant's proposed variability. Additionally, the very small sample

number, low RIN values for many samples, and different skip numbers across various exon deletion subgroups, do not allow a clear interpretation of a trend in dystrophin skip product increase between groups.

Dystrophin expression by IFA:

The results of dystrophin analysis by IFA were not supportive for the treatment group. The relative intensity was increased in maximum number of subjects in the placebo group and only 1 subject in the 6 mg/kg group (Table 24).

Table 24 Summary of Immunofluorescence Assay and Western Blot Qualitative Muscle Biopsy Data

Parameter/ Testing Method	Result	Number (%) of Subjects		
		Placebo (combined) (N=16)	Drisapersen 3 mg/kg (N=17)	Drisapersen 6 mg/kg (N=18)
Relative Intensity (All muscles)				
Week 24 Immunofluorescence assay (IFA)	n	12	11	13
	Increase	7 (58)	5 (45)	1 (8)
Western blot (WB) Week 24	n	5	5	1
	Increase	0	1 (20)	0

Source: Adapted from page 99

Predefined criteria for increase: (>4% increase compared to baseline)

Based on an initial analysis at Week 24, the mean percent increase from baseline in dystrophin were observed in both the drisapersen 3 mg/kg/week group (2%) and placebo group (6%) compared with a decrease in the drisapersen 6 mg/kg/week group (-3%) as shown in Table 25.

Table 25 Summary of Dystrophin Intensity Measurement by IFA (change from Baseline to Week 24)

Parameter		Placebo (combined) (N=16)		Drisapersen 3 mg/kg (N=17)		Drisapersen 6 mg/kg (N=18)	
		n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Non-Qualified Mean Percentage Change (%)	Week 12	0	NA	2	-2 (6)	2	-0.5 (5)
	Week 24	12	6 (10)	11	2 (11)	13	-3 (6)
	Week 36	0	NA	0	NA	0	NA
Non-Qualified Q90 Percentage Change (%)	Week 12	0	NA	2	-6 (4)	2	-2 (3)
	Week 24	12	8 (13)	11	-0.2 (11)	13	- 4 (8)
	Week 36	0	NA	0	NA	0	NA

Source: Study DMD114876 report, page 100

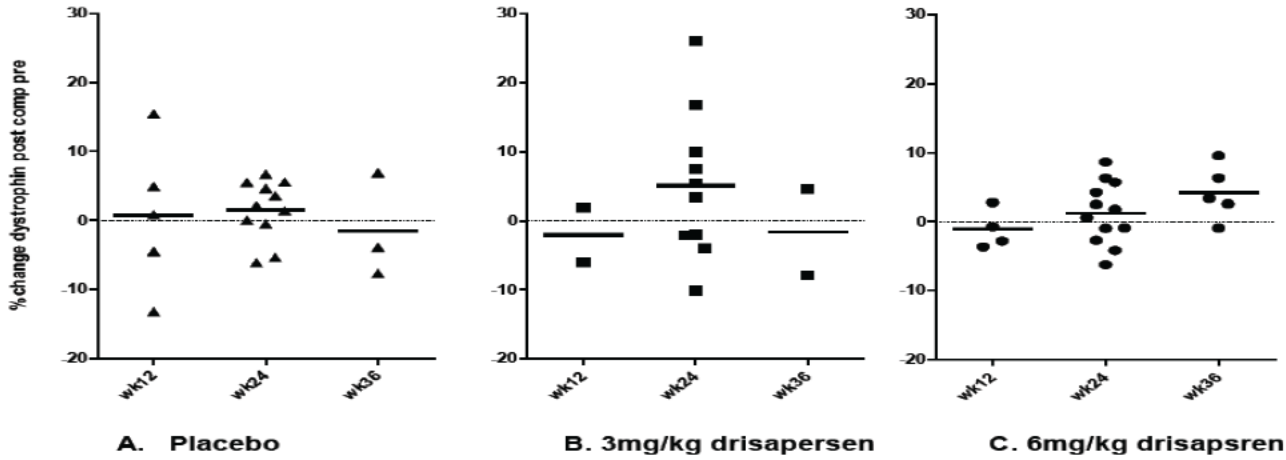
After this initial analysis, due to the large variability, no difference between the treated and placebo group and large changes in spectrin between 2 biopsies, the applicant further investigated the variability and presented the results in a separate report. A repeat analysis of these biopsies was conducted in 2-3 experiments. An average of the 2-3 repeat experiments was reported for each subject. These were used to calculate the non-qualified mean percentage change as shown in Table 26 and Figure 14. The highest increase at Week 24 was observed in the 3 mg/kg group.

Table 26 Summary if dystrophin intensity measurement (by average by 2-3 experiments for each subject)

Parameter	Visit	Placebo (N=16)		Drisapersen 3 mg/kg (N=17)		Drisapersen 6 mg/kg (N=18)	
		n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Non-Qualified Mean Percentage Change (%)	wk12	5	1% (11%)	2	-2% (6%)	4	-1% (3%)
	wk24	11	2% (4%)	10	5% (11%)	12	1% (4%)
	wk36	3	-2% (8%)	2	-2% (9%)	5	**4% (4%)**
Non-Qualified Q90 Percentage Change (%)	wk12	5	1% (17%)	2	-6% (5%)	4	-2% (1%)
	wk24	11	1% (6%)	10	5% (11%)	12	0% (6%)
	wk36	3	0% (14%)	2	-6% (3%)	5	-13% (12%)

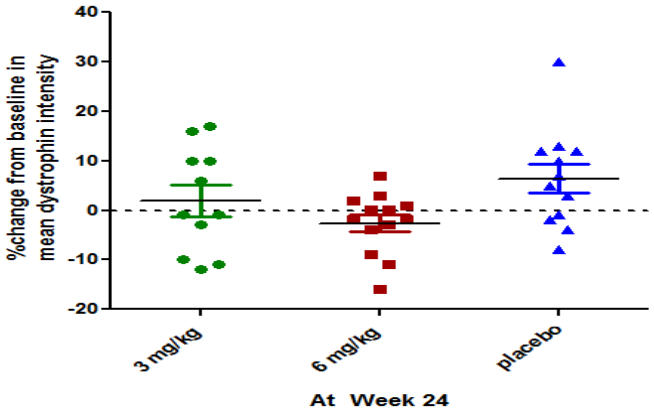
Source: DMD114876-LAB-01 report, page

Figure 14 % change in mean dystrophin intensity in individual subjects from an average of 2-3 experiments (IFA)



<u>Reviewer's Comment:</u> The applicant's scatter plot in Figure 14 shows larger variability in the % change in mean dystrophin intensity in the 3 mg/kg group (-10% to 26%) compared to the 6 mg/kg group (-4% to 9%), driving a higher mean % change for the 3 mg/kg group at Week 24. There is also no appreciable differences in dystrophin expression between placebo (-6 to 7%) and 6 mg/kg group (-4% to 9%). While there appears to be an upward trend in the mean values, the values are within the known assay variability and not apparently or statistically significant. In addition, no dose was given beyond 24 weeks, hence the reason for the upward trend observed is unclear. The scatter plot based on their original analysis is shown in Figure 15

Figure 15: % change in mean dystrophin intensity in individual subjects from original experiment (IFA)



OBP Reviewer Dr. Rao's Comment on IFA:

The applicant states that the inter-assay reproducibility of their IFA assay between experiments for placebo and drisapersen-treated subjects combined was 5% and ranged between 0-16% for the study. It is not clear if the mean values reported in Table 26 that are below 5% represent biologically-relevant responses or expected assay variability. There also appear to be several critical deficiencies in the applicant's design of experiments that preclude an interpretable assessment of dystrophin increase: (1) the Applicant states that the IFA analyses were repeated up to 3 times to "*investigate further the inter-biopsy and inter-assay precision from one* subject 027; however repeated analyses were carried out for several other subjects without any accompanying justification regarding why 2 or, in some cases, 3 replicates were obtained, (2) the Applicant states that the operators and managers were blinded to the treatment groups at the time of the 2013 analysis, after which the treatment regime was unblinded. The IFA repeat analyses were carried out in 2014 and after the study was unblinded, (3) in the case of each of the 2nd or 3rd replicate values, it was noted that the placebo samples showed lower dystrophin intensity values and the treatment samples showed higher values in the re-analysis. In the absence of a systematic, consistent, and prospective design of experiment, it may not possible to conclude that the repeated analyses generated unbiased and robust mean dystrophin values. See Appendix B for additional deficiencies.

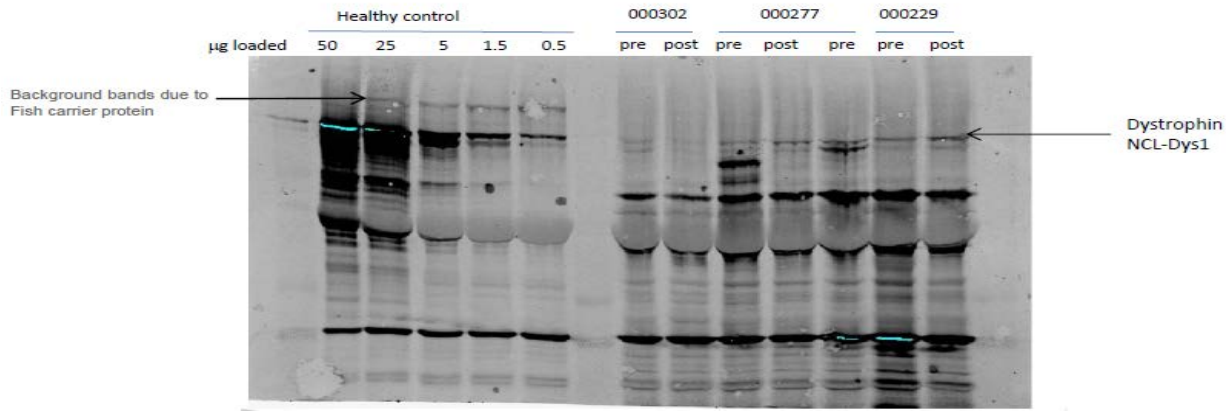
Dystrophin expression by WB:

The applicant has provided limited western blot analysis data for this study. They claim that in most instances the biopsies were of too poor quality to generate data. In the 3 mg/kg/wk group, 5 subjects were anlayzed and one showed an increase in dystrophin protein. The one subject in the 6 mg/kg/wk group that was analyzed did not show an increase.

OBP Reviewer Dr. Rao's Comment on WB:

In addition to the poor quality of biopsies and very low sample number, the Applicant chose to examine the 11 subjects for western blotting whose samples were originally deemed unsuitable for IFA analysis.

The applicant did include a loading control healthy sample in their western blots and used beta3-spectrin as a loading control. However, there is no clear trend showing an increased band in post-treatment samples. The dystrophin band appears to diminish in some post-treatment samples (e.g. subject 277). Image below was provided by the Applicant upon request for raw data from this study. While the applicant has not compared their dystrophin values to the healthy control samples on the same gel, in most cases the dystrophin band appears to be at or lower than the lowest dilution of healthy control sample tested. The applicant was asked to clarify how the dystrophin values compared to the healthy controls on the same gels. They stated that while it is not possible to accurately calculate the relative dystrophin signal due to a lack of linearity at the low levels of signal from the DMD samples, they estimate that the dystrophin expression they observed is generally around 0.3% or below of the highest control dilution. They further state that only 4/18 *samples* tested showed dystrophin levels above their lower limit of detection of 1% of normal, and that those 4 samples with 2.1-4.1% of normal dystrophin levels did not show an appreciable treatment effect when compared to their corresponding pre-treatment sample.



Persistence of Effect

<u>Reviewer's Comment:</u> One of the objectives of this study was to determine the persistence of effect during the drug free observation period from week 25- Week 48. The treatment difference was maintained at Week 48 for the 6mg/kg group.
Also interesting to note that the change from baseline was not maintained for the 6 mg/kg group in Study DMD114117, which in treatment was given for 48 weeks. So it is unclear if the persistence of effect observed in this study is a true treatment effect or the natural variation in the DMD population.

<u>Reviewer's Analysis and Discussion:</u>

The study results in general appear weak, some weak trends in favor of treatment observed were:

- **The primary endpoint (change from baseline in 6MWD at Week 24) had a numerical advantage on 6MWD with a treatment difference of placebo of 27 m for the 6mg/kg dose, but the study was negative (p=0.07).**

- **The reduction in creatinine kinase was in favor of the drisapersen treated groups. There was a dose related response in the reduction of CK at week 24, with a greater decline in the 6 mg/kg group compared to the 3 mg/kg group, but only the 3 mg/kg group continued to decline during the drug free period at Week 28.**

The weaknesses of the observed results from Study DMD114876 are:

- **Based on the pre-specified primary efficacy analysis for the change from baseline 6MWD, the study was negative with a p-value of 0.07**
- **Removing one subject in the placebo group who was unblinded due to a hospital visit, the treatment difference was 19 m, p=0.21**
- **There was no dose response:**
  - **6 mg/kg/week was superior than placebo (27m)**
  - **3 mg/kg/week was worse than placebo (-9 m)**

  This could be suggestive of noise in the data or difference in disease characteristics of the two dose groups as discussed earlier.
- **The secondary endpoints in this study were not supportive of the primary endpoint. There was no dose related trends in the secondary endpoints, with 3 mg/kg trending better compared to 6mg/kg in some endpoints (10m walk/run, 4 stair climb, muscle strength, NSAA).**
- **Potential partial unblinding to the assigned treatment due to injection site reactions: Unblinding could affect the performance of 6MWD, which is an effort dependent endpoint. The incidence and the duration of injection site reactions was the largest for the 6 mg/kg group and the least for placebo.**
- **The dystrophin expression (IFA and WB) did not favor treatment benefit. The dystrophin expression as evaluated by IFA showed the similar response in the placebo group and 6 mg/kg group. The RT-PCR exon skipping data showed higher percent of exon skip subjects in favor of the 6mg/kg group, but this was not supported by IFA analysis. The WB analysis did not show any treatment response.**

6.3. Study DMD114044

6.3.1. Study Design

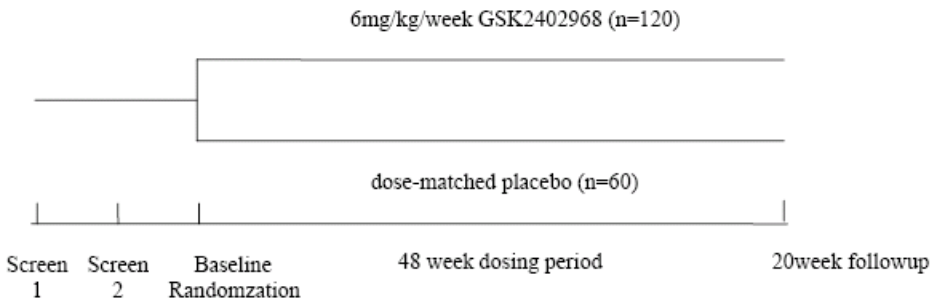
Overview and Objective

This study was designed to assess the efficacy of drisapersen 6 mg/kg once weekly for 48 weeks in ambulant subjects with DMD compared to placebo. The secondary objectives were to assess safety, tolerability, PK and impact on quality of life.
Studied period**:** 02 December 2010 to 28 June 2013
Study center(s): 44 centers in 19 countries: Argentina, Belgium, Brazil, Canada, Chile, Czech Republic, Denmark, France, Germany, Italy, Japan, Korea, Netherlands, Norway, Poland, Russia Federation, Spain, Taiwan, and Turkey.

Trial Design

This phase III, randomized, double-blind, parallel-group clinical study similar in design to Studies DMD114117 and DMD114876, with the exception of primary endpoint assessments at Week 48. Any differences will be outlined in this section. Subject completing this study entered an open label extension (Study DMD114349). The study design schematic is shown in Figure 16.

Figure 16 Study design schematic for Study DMD114044



Population: N= 186 DMD boys with a mutation corrected by exon 51 skipping. The study was designed to have 90% power to detect a difference in 6MWD between drisapersen and placebo of 30 meters, assuming a common standard deviation of 55 meters.
Key Inclusion/Exclusion Criteria: Same as Study DMD114117 and DMD114876, with the exception of:

- There was no restriction on ability to rise from floor (in $\leq$ 7 seconds for Study DMD114117, and $\leq$ 15 seconds for Study DMD114876). Subjects with any rise time could be enrolled in this study.

Dosing Regimen:
Subjects were randomized to the following in 2:1 ratio using Interactive Voice Response System. Similar blinding approaches were adopted as the Phase 2 studies.

- 6 mg/kg/week SC drisapersen for 48 weeks (N=125)
- SC placebo for 48 weeks (N=61)

To minimize injection site reactions, rotation of site on a weekly basis was recommended. Abdomen, arms, thighs, back and buttocks were all used as injection site.
Applicant's Dose Rationale: Prior to randomization in this study, 12 subjects from open label study DMD114673 had received 6 mg/kg/week for 48 weeks. A mean change from baseline in the 6MWD at Week 24 was 37 m (range -58 m to +115 m). The applicant considered this supportive of the choice of the dose. In addition, due to early signs of potential subclinical renal effects (mild proteinuria) in the open label study and the preclinical pro-inflammatory findings (including data from the 39 week monkey study), 6 mg/kg was considered to be the maximum tolerated dose (MTD) and selected for this study.

Reviewer's Comment: This study was initiated 3 months after the initiation of the 48 week Study DMD114117.

Study Endpoints

The primary efficacy endpoint was 6MWD at week 48. 6MWD was assessed at screening (1 and 2), randomization, at weeks 24, 36 48 or follow-up.
The secondary efficacy endpoints were same as Study DMD114117 and DMD114876. Some of the differences between the endpoints were:

- For pulmonary function tests, MIP, MEP (Study DMD114117 only) and sniff nasal pressure (Study DMD114876 only) were not measured in this study.
- The quality of life assessments in this study were:
  - Pediatric Quality of Life Neuromuscular module (also on Study DMD114117)
  - Clinician Global Impression of Improvement (CGI-I) (also in study DMD114876)
  - Health Utilities Index
  - Activities of Daily Living

Key Secondary Endpoints:

1. Change from baseline in the NSAA linearized score
2. Change from baseline in the 4-stair climb (ascent) velocity
3. Change from baseline in the 10-meter walk/run velocity

Other exploratory endpoints:

- MRI and DEXA

Statistical Analysis Plan

Primary Analysis: Change from baseline in the 6MWD at week 48 was analyzed for the OC dataset on ITT population using MMRM with fixed effects of treatment, visit, treatment by visit interaction, country grouping, and continuous fixed covariates of baseline 6MWD and baseline 6MWD by visit. Other supportive information was derived from Week 12, 24, and 36. The covariates assessed were: country group, baseline 6MWD, age, age group (≤7 and >7 years), corticosteroid regimen (Continuous or Intermittent), Baseline rise from floor group (Less than or equal to 7 seconds or greater than 7 seconds), 117 Data dissemination group (Week 48 visit before or after 117 dissemination), country, and race. Statistical significance tests were 2 sided.
Sensitivity analyses were also similar to Study DMD114117 and DMD114876.
Secondary Analysis: If a statistically significant treatment difference at the 5% level was observed for the primary efficacy endpoint, then the key secondary endpoints were tested in a hierarchical manner. For all other endpoints no adjustment for multiplicity was made and all were performed at α of 5% and considered supportive.

Protocol Amendments

Amendment 1 (Sep 2010)	• If subjects become non ambulatory and are unable to perform the 6MWD assessment for this reason, their distance will be imputed to be 0m for the purposes of analysis • Clarified that the primary analysis will be on OC data. • Sensitivity analyses will be on LOCF data • Efficacy analysis using PP population will be a sensitivity analysis • MMRM analysis for PP population will be a sensitivity analysis.

	• ANCOVA with the LOCF and OC dataset will be carried out for the 6MWD at week 48
Amendment 2 (21 Jun 2011)	• Allow subjects who withdrew for safety reasons to enter the extension study • MRI sub-study as requested by EMA. This would be performed only in Argentina and Brazil due to logistical and timing issues

Reviewer's Comment: Amendments related to study analysis were made prior to initiation of enrollment

Data Quality and Integrity: Sponsor's Assurance

Management of clinical data was performed in accordance with GSK standards. The study was conducted in accordance with ICH GCP (ICH E3 and E6) and applicable country-specific requirements. Written commitments were obtained from investigators to comply with GCP. Study was conducted with written informed consent from subjects and their parents.

6.3.2. Study Results

Patient Disposition

A total of 181 subjects completed the study (Table 27).

Table 27 Summary of subject disposition

Subject Status	Number (%) of Subjects		
	Placebo (N=61)	Drisapersen 6 mg/kg/week (N=125)	Total (N=186)
Completed	60 (98)	121 (97)	181 (97)
Withdrawn	1 (2)	4 (3)	5 (3)
Primary reason for study withdrawal			
Adverse event[a]	0	2 (2)	2 (1)
Withdrew consent	0	2 (2)	2 (1)
Protocol deviation[b]	1 (2)	0	1 (<1)

Source: Study DMD114044 report, page 64
a. An AE of glomerulonephritis leading to discontinuation was reported in 1 subject (Subject 527). Intracranial venous sinus thrombosis and spinal pain AEs leading to discontinuation were reported for 1 subject (Subject 1270).
b. Subject 1266 in the placebo group had mutation not correctable by exon 51 skipping

Protocol Violations/Deviations

A total of 7 (11%) subjects in the placebo group and 22 (18%) subjects in the drisapersen group had a major protocol deviation. Summary of major protocol violations leading to exclusion from the PP population is shown in Table 28.

Table 28 Protocol Deviations

	Number (%) of Subjects		
	Placebo (N=61)	Drisapersen 6 mg/kg/week (N=125)	Total (N=186)
ITT Population	61 (100)	125 (100)	186 (100)
PP Population	54 (89)	103 (82)	157 (84)
Total Number of Subjects with Major Protocol Deviations	7 (11)	22 (18)	29 (16)
Mutation not correctable by exon 51 skipping.	1 (2)	0	1 (<1)
Not able to complete 6MWD test with minimal distance of at least 75 m at each pre-drug visit. In addition, results must be within 20% of each other at each pre-drug visit.)	1 (2)	6 (5)	7 (4)
Symptomatic cardiomyopathy.	0	2 (2)	2 (1)
Use of prohibited concomitant medication	2 (3)	9 (7)	11 (6)
Significant change in corticosteroid regimen	2 (3)	2 (2)	4 (2)
Subjects not adequately complying with dosing specifications of the study	1 (2)	6 (5)	7 (4)

Source: Study DMD114044 report, page 65

Reviewer's Comment: A sensitivity analysis removing protocol violators did not change the overall conclusions, but treatment difference was reduced (Table 32).

Table of Demographic Characteristics

Most demographic characteristics were similar across treatment group, with numerically higher weight in drisapersen group (Table 29).

Table 29 Summary of demographic characteristics

	Placebo (N=61)	Drisapersen 6 mg/kg/week (N=125)	Total (N=186)
Age (yrs)			
Mean (SD)	8.0 (2.4)	8.3 (2.4)	8.2 (2.4)
Median	8.0	8.0	8.0
Min., Max.	5, 16	5, 16	5, 16
Ethnicity, n (%)			
Hispanic/Latino	10 (16)	23 (18)	33 (18)
Not Hispanic/Latino	51 (84)	102 (82)	153 (82)

Race, n (%)			
African American/African Heritage	1 (2)	0	1 (<1)
Asian - Central/South Asian Heritage	1 (2)	3 (2)	4 (2)
Asian - East Asian Heritage	3 (5)	6 (5)	9 (5)
Asian - Japanese Heritage	5 (8)	9 (7)	14 (8)
Asian - South East Asian Heritage	0	2 (2)	2 (1)
White - Arabic/North African Heritage	4 (7)	5 (4)	9 (5)
White - White/Caucasian/European Heritage	46 (75)	95 (76)	141 (76)
White - Mixed Race	0	1 (<1)	1 (<1)
Mixed Race	1 (2)	4 (3)	5 (3)
Height (cm)			
Mean (SD)	122 (10)	124 (11)	NA
Median	122	123	NA
Min., Max.	102, 145	101, 148	NA
Weight (kg)			
Mean (SD)	27(7)	30 (10)	NA
Median	24	27	NA
Min., Max.	17, 46	17, 68	NA

Source: Study DMD114044 report, page 67

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Mean baseline values for the 6MWD was lower, time since first corticosteroid taken, time since first symptoms and time since diagnosis were all was numerically longer in the drisapersen group than in the placebo group.

Table 30 Summary of Muscular Dystrophy Disease Baseline Characteristics

	Placebo (N=61)	Drisapersen 6 mg/kg/week (N=125)	Total (N=186)
Time Since First Symptoms (months)[a]			
n	58	122	180
Mean (SD)	66.7 (31)	71.8 (31.5)	70.2 (31.5)
Median	60.8	70.2	66.8
Min., Max.	11, 168	12, 176	11, 176
Time Since Diagnosis (months)[a]			
n	61	125	186
Mean (SD)	54.2 (32.8)	58.0 (35.2)	56.7 (34.4)
Median	49.8	54.5	53.1
Min., Max.	6, 148	6, 163	6, 163
Time Since First Corticosteroid Taken (months)[a]	61	125	186
n	29.1 (25.8)	35.6 (28.9)	33.5 (28.1)
Mean (SD)	18.9	26.6	25.6
Median	7, 135	6, 146	6, 146
Min., Max.			

Corticosteroid Regimen, n (%)[b]			
n	61	125	186
Continuous	52 (85)	108 (86)	160 (86)
Intermittent	9 (15)	17 (14)	26 (14)
6MWD (m)	61	125	NA
Mean (SD)	348 (92)	337 (95)	NA
Method of Diagnosis, n (%)[c]			
n	61	125	186
Clinical symptoms	56 (92)	110 (88)	166 (89)
Muscle biopsy	21 (34)	47 (38)	68 (37)
Genetic testing	61 (100)	125 (100)	186 (100)
Multiplex Ligation-dependent Probe Amplification	59 (97)	117 (94)	176 (95)
Comparative Genomic Hybridisation	0	7 (6)	7 (4)
Single Condition Amplification/Internal Primer	1 (2)	1 (<1)	2 (1)
Other	1 (2)	0	1 (<1)
EXON Mutation, n (%)			
n	61	125	186
DMD 45-50 deletion	16 (26)	40 (32)	56 (30)
DMD 47-50 deletion	1 (2)	0	1 (<1)
DMD 48-50 deletion	7 (11)	26 (21)	33 (18)
DMD 49-50 deletion	20 (33)	31 (25)	51 (27)
DMD 50 deletion	5 (8)	11 (9)	16 (9)
DMD 52 deletion	10 (16)	16 (13)	26 (14)
Other	2 (3)	1 (<1)	3 (2)

Source: Study DMD114044 report, page 68

Reviewer's Assessment of baseline characteristics:

The baseline characteristics were generally balanced across treatment groups, with a small number of subjects with greater functional impairment in the drisapersen group based on age and 6MWD. The mean time since first diagnosis and time since first symptoms was greater in the drisapersen group. For a large study these differences are not likely to adversely affect the study results.

- **Impact of age distribution: The subjects <7 years are balanced between the two groups. Subjects ≥ 7 years are also balanced between the two groups, but there were 17% subjects >11 years in the drisapersen group compared to 11% in the placebo group.**
- **Impact of 6MWD: Mean baseline 6MWD was lower in the drisapersen group. I looked at the distribution of 6MWD in the treatment groups. There were higher number of subjects with baseline 6MWD <150m and in between 250-300m in the drisapersen group (18%) compared to placebo (12%), and a higher % of subjects with 6MWD greater than 350 m in the placebo group (54%) compared to drisapersen group (49%).**

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

About 60 (98%) subjects in the placebo group and 119 (95%) subjects in the drisapersen group were >80% compliant. The total dose and duration of exposure were similar.

Efficacy Results - Primary Endpoint

Applicant's Analysis: A statistically non-significant (p=0.415) treatment difference of 10.3m for drisapersen over placebo at week 48 was observed for the primary endpoint change from baseline in 6MWD.

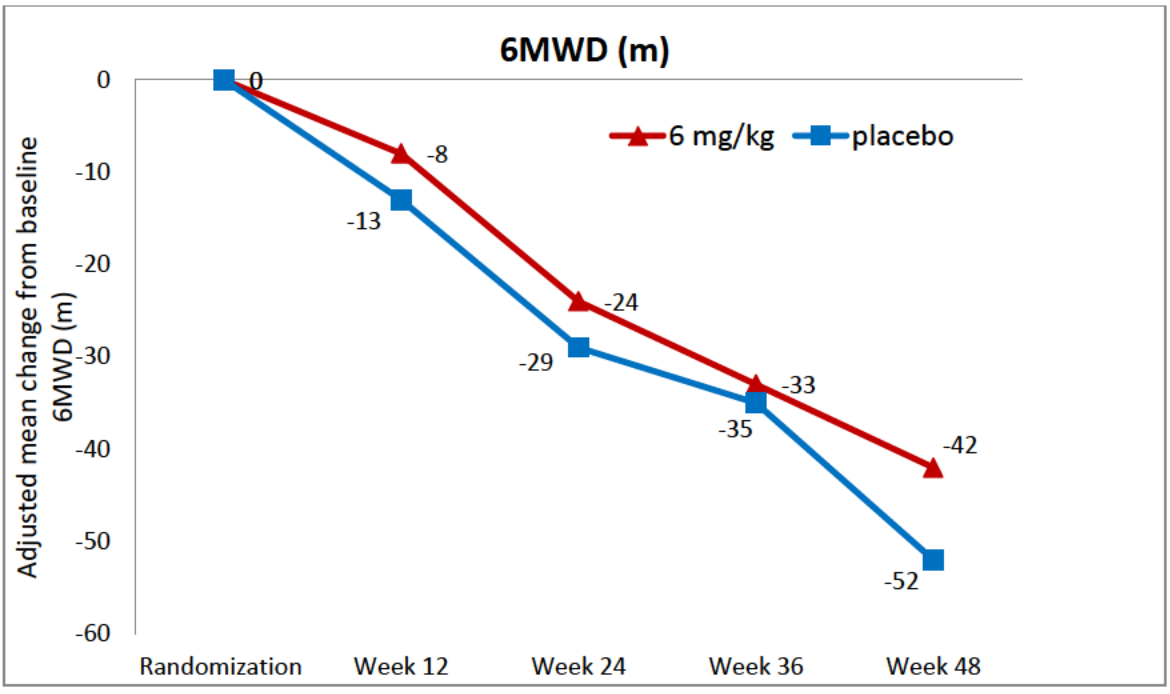
Table 31 MMRM Analysis of change from baseline in 6MWD (m)

	Placebo (N=61)	Drisapersen 6 mg/kg/week (N=125)
Baseline		
n	61	125
Mean (SD)	348 (92)	337(95)
Week 48		
n	59	117
Adjusted mean change (SE)	-52 (10)	-42 (7)
Adjusted mean difference vs. placebo		10
95% CI		(-15, 35)
p-value		0.42

Source: Study DMD114044 report, page 77

I generated the following Figure that shows the time course of the change from baseline for drisapersen 6 mg/kg/week and placebo at each visit.

Figure 17 MMRM Analysis of change from baseline in 6MWD (m)



None of the covariates evaluated showed a significant treatment interaction. Exon mutation and baseline CK were fitted as covariates retrospectively and did not show any significant interaction as well.

Clinical Review (Efficacy)
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Sensitivity Analyses:

Most sensitivity analyses were consistent with the primary analyses and gave similar treatment differences, with the exception of MMRM analysis with the PP population (removing protocol violators), where the treatment difference was reduced to **4.9 m (p=0.703) (Table 32)**

Table 32 Sensitivity Analyses for Change from Baseline in 6MWD (m) at Week 48 (ITT Population)

Analysis/Treatment	n	Adjusted Mean Change from Baseline (SE)	Treatment Difference[a]	95% CI	p-value
MMRM OC (ITT)[b]					
Placebo	59	-52 (10)			
Drisapersen 6 mg/kg/wk	117	-42 (7)	10	(-15, 35)	0.42
MMRM OC (PP)[b]					
Placebo	53	-45 (10)			
Drisapersen 6 mg/kg/wk	99	-40 (7)	5	(-20, 30)	0.70
ANCOVA OC (ITT)[c]					
Placebo	59	-50 (11)			
Drisapersen 6 mg/kg/wk	117	-38 (8)	12	(-14, 37)	0.36
ANCOVA LOCF (ITT)[c]					
Placebo	60	-50 (10)			
Drisapersen 6 mg/kg/wk	125	-38 (7)	11	(-13, 36)	0.36
ANCOVA Multiple Imputed (MAR approach) (ITT)[d]					
Placebo	59	-50 (10)			
Drisapersen 6 mg/kg/wk	117	-40 (8)	10	(-15, 35)	0.43
ANCOVA Multiple Imputed (CIR approach) (ITT)[d]					
Placebo	59	-50 (10)			
Drisapersen 6 mg/kg/wk	117	-40 (8)	10	(-15, 35)	0.44

Additional analyses on 6MWD:

1. Percent-predicted 6MWD: The percent predicted 6MWD in DMD provides an estimate of performance relative to a healthy control population to account for age and development differences. An increase in the percent-predicted 6MWD is consistent with functional improvement. The results of this analysis showed a 2 % difference between the placebo and drisapersen group at Week 48 (95% CI: -2, 6) which was not statistically significant (p=0.32)
2. Change from baseline in 6MWD by response category
   At week 48, the percent of subjects with ≥ 30 m change in 6MWD was 18% in the drisapersen group and 12% in the placebo group. The percent of subjects with ≥ 60 m change in 6MWD were similar in the two groups.
3. Time to persistent 10% decrease in 6MWD: 43% subjects show persistent 10% decrease in placebo compared to 36% subjects in drisapersen group.
4. Sub-group Analyses: Post-hoc analyses on various subgroups were conducted. Only sub-groups that showed a greater treatment difference at week 48 in the change from baseline in 6MWD over placebo are summarized in Table 33. These large numbers of post-hoc analyses in smaller number subjects are uninterpretable. Sub-group analysis (as summary statistics) in subjects ≤ 7 years and > 7 years was pre-specified, other sub-group analyses were post hoc. Subjects

>7 years showed a treatment difference of 7 m, whereas subjects less than 7 years showed a treatment benefit of 21 m (Table 33). Other sub-group analyses showing treatment difference in favor of 6 mg/kg is summarized in the following Table.

Table 33 Sub-group Analyses

Treatment	N	Baseline Mean (SD)	n	Adjusted Mean Change from Baseline (SE) at Week 48	Treatment Difference	95% CI
Age ≤7 years at Baseline (pre-specified)						
Placebo	29	383 (66)	29	-25 (11)	21	(-6, 48)
Drisapersen 6 mg/kg/wk	51	368 (65)	50	-4 (8)		
Rise from Floor >7s at Baseline						
Placebo	26	318 (77)	25	-88 (16)	21	(-20, 61)
Drisapersen 6 mg/kg/wk	47	307 (75)	43	-67 (12)		
Able to Stand from Supine at Baseline (Rise from Floor Grade >1)						
Placebo	55	363 (82)	53	-43 (10)	15	(-10, 40)
Drisapersen 6 mg/kg/wk	106	360 (80)	102	- 28 (7)		
≤330 m at baseline						
Placebo	22	256 (67)	21	-93 (22)	18	(-32, 69)
Drisapersen 6 mg/kg/wk	57	253 (66)	50	-75 (14)		
Centers previously enrolled in other studies						
Placebo	9		9	-109(25)	62	(-2, 126)
Drisapersen 6 mg/kg/wk	17		17	-47(18)		

Change from baseline by country grouping showed largest treatment difference in Northern Europe and Russia-Eastern Europe grouping, but the number of subjects was small.

5. Time to a 25, 50% and 75 % decrease in 6MWD: These similar across treatment groups.
6. 6MWD in subjects with Rise from Floor ≤7 seconds: In this study there were no restrictions on rise from floor time. As a post-hoc analysis in this subgroup, the treatment difference (5m) was smaller than in the DMD114044 population as a whole (10m). In fact the treatment difference was larger in subjects with rise from floor >7 seconds (21m). The applicant indicates that the greater range of rise from floor values at baseline was not the primary reason for the differing results (Table 34).

Table 34: MMRM Analysis of Change from baseline in 6MWD at week 48 by baseline Rise from Floor

Treatment	N	Baseline Mean (SD)	n	Adjusted Mean Change from Baseline (SE) at Week 48	Treatment Difference	95% CI
Rise from Floor ≤7s at Baseline						
Placebo	29	404 (62.520)	28	-4 (10)	5	(-18, 28)
Drisapersen 6 mg/kg/wk	59	402 (55.540)	59	1 (7)		
Rise from Floor >7s at Baseline						
Placebo	26	318 (77)	25	-88 (16)	21	(-20, 61)
Drisapersen 6 mg/kg/wk	47	307 (75)	43	-67 (12)		

Source: Study DMD114044 Study Report, page 83

Data Quality and Integrity - Reviewers' Assessment

There were no issues with data quality or integrity.

Efficacy Results - Secondary and other relevant endpoints

No significant treatment differences or consistent trends in favor of drisapersen were observed for any key or other secondary endpoints (Table 35)

Table 35 Secondary endpoints

Treatment	n	Baseline Mean (SD)	Adjusted Mean Change from Baseline (SE) at Week 48	Treatment Difference	95% CI	p-value
Key Secondary Efficacy Endpoints						
Linearized NSAA Total Score						
Placebo	58	58.4 (17.71)	-6.7 (1.43)			
Drisapersen 6 mg/kg/wk	117	56.6 (18.85)	-7.2 (1.01)	-0.53[a]	(-3.95, 2.88)	0.757
4 Stair Climb Ascent Velocity (stairs/s)						
Placebo	55	0.88 (0.573)	-0.12 (0.049)			
Drisapersen 6 mg/kg/wk	111	0.86 (0.658)	-0.14 (0.035)	-0.021[a]	(-0.137, 0.095)	0.718
10 m Walk/Run Velocity (m/s)						
Placebo	58	1.57 (0.542)	-0.20 (0.050)			
Drisapersen 6 mg/kg/wk	117	1.54 (0.575)	-0.21 (0.035)	-0.009[a]	(-0.129, 0.111)	0.881
Other Secondary Efficacy Endpoints						
Rise from Floor (s)[c]						
Placebo	44	13.41 (15.882)	7.48 (2.080)			
Drisapersen 6 mg/kg/wk	91	12.34 (14.984)	6.36 (1.463)	-1.115[b]	(-6.097, 3.866)	0.658
4 Stair Climb Descent Velocity (stairs/s)						
Placebo	55	0.98 (0.601)	-0.15 (0.052)			
Drisapersen 6 mg/kg/wk	109	1.02 (0.634)	-0.11 (0.037)	0.041[a]	(-0.082, 0.164)	0.513
Muscle Strength Total Score (lbs)						
Placebo	58	98.55 (30.527)	-1.21 (2.729)			
Drisapersen 6 mg/kg/wk	118	102.49 (34.941)	-2.18 (1.926)	-0.965[a]	(-7.446, 5.516)	0.769
Creatine Kinase (IU/L)						
Placebo	60	11901.1 (7133.32)	-1228.5 (500.59)		(-5232.21,	
Drisapersen 6 mg/kg/wk	118	10956.5 (7316.07)	-5273.5 (359.05)	-4044.99[b]	-2857.77)	<0.001

Source: Adapted from Study DMD114044 report

There were no meaningful changes in pulmonary functions tests (not shown in the Table).

Creatine Kinase:

A statistically significant treatment difference in favor of drisapersen in change from baseline in creatinine kinase serum concentration was observed at week 48 with a 48% decrease in absolute mean CK in the drisapersen group compared to 10% in the placebo group.

Table 36 Summary of MMRM analyses of Serum creatine kinase (IU/L)

Treatment	N	Baseline Mean (SD)	n	Adjusted Mean Change from Baseline (SE) at Week 48	Treatment Difference	95% CI P-value
Placebo	61	11901 (7133)	60	-1228 (500)	-4044	(-5232, -2858) <0.001
Drisapersen 6 mg/kg/wk	125	10956 (7316)	118	-5273 (359)		

Source: page 91

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Post-hoc analyses on CK: Post-hoc analyses showed a greater decline in CK compared to placebo in subjects ≤7 years vs. > 7 years, consistent with a larger treatment difference with 6MWD observed in ≤7 years (Table 37).

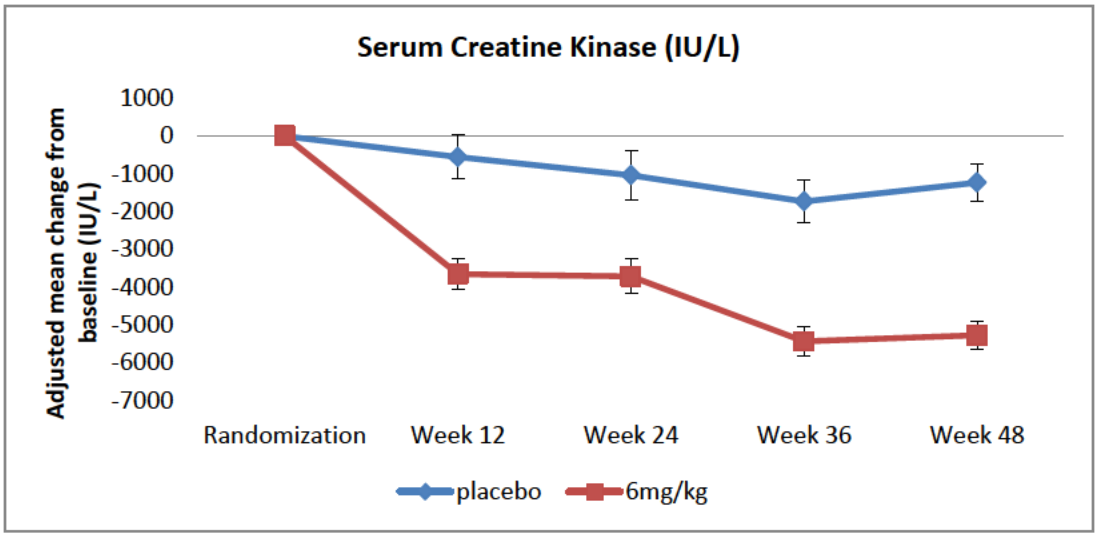
Table 37 MMRM analysis of CK based on age group

Treatment	N	Baseline Mean (SD)	n	Adjusted Mean Change from Baseline (SE) at Week 48	Treatment Difference	95% CI
≤7 years at baseline						
Placebo	29	15471 (6834)	29	-1314 (831)		
Drisapersen 6 mg/kg/wk	51	15626 (8422)	49	-7230 (613)	-5916	(-7890, -3942)
>7 years at baseline						
Placebo	32	8666 (5794)	31	-1439 (570)		
Drisapersen 6 mg/kg/wk	74	7738 (4075)	69	-3589 (407)	-2149.	(-3455, -845)

Source: Study DMD114044 report, page

I generated the following Figure 18 that shows the time course of reduction in CK.

Figure 18 MMRM analysis of change from baseline in CK



CGI-I, PedsQL, Health Utility Index Scores, and Activities of Daily Living: A total of 1 (2%) subject in the placebo group and 12 (10%) subjects in the drisapersen group were considered responders (much improved or very much improved) on the CGI-I at Week 48. Two (4%) subjects in the placebo group and 23 (20%) subjects in the drisapersen group minimally improved on the CGI-I at Week 48. There were no clinically meaningful treatment differences between drisapersen and placebo for the PedsQL Neuromuscular Module, HUI health outcomes assessments and Activities of Daily Living.

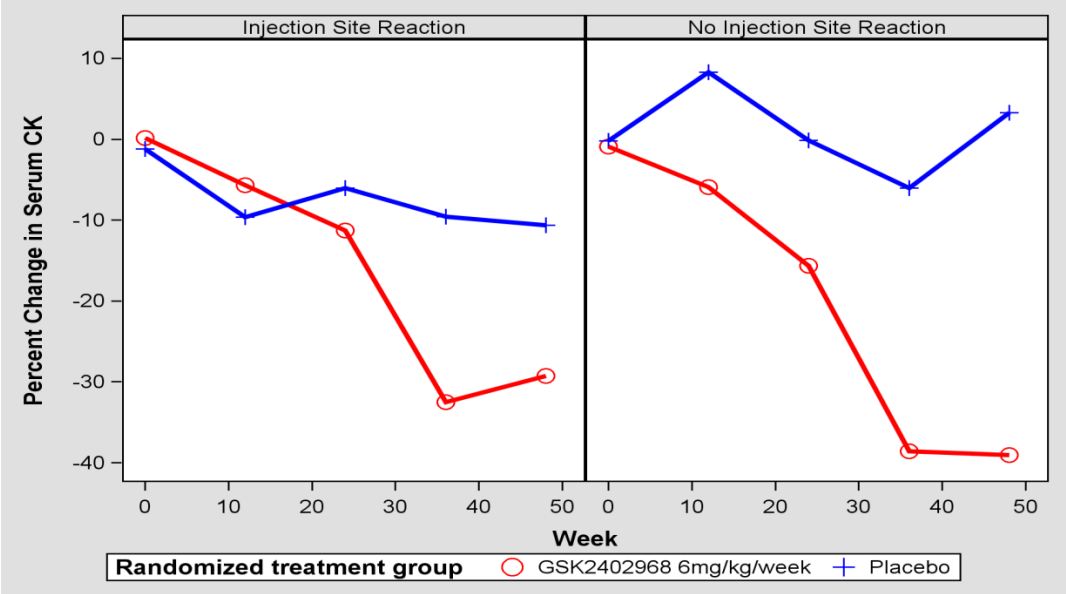
Time to loss of ambulation: A total of 6 (10%) subjects in the placebo group and 15 (12%) subjects in the drisapersen group lost ambulation during the study. A Kaplan-Meier analysis of Time to loss of ambulation did not show any difference (Figure not shown). There was a complete overlap of the 95%

confidence interval between treatment groups. Subjects who lost ambulation had a higher mean age in both treatment groups (placebo: 9 years; drisapersen: 10 years) compared with subjects who remained ambulant during the study (placebo: 8 years; drisapersen: 8 years).

Reviewer's Analysis and Comment:

Since the difference in CK between the treatment and placebo groups were statistically significant (p<0.001), I wanted to explore if this difference was due to inactivity resulting from injection site reactions. The reduction of CK was greater in the treatment group compared to placebo whether subjects had an injection site reaction or not, as depicted in Figure 19. The level of activity/inactivity could not be assessed by patient reported outcomes or other means. Overall CK was reduced by 32% in the drisapersen group.

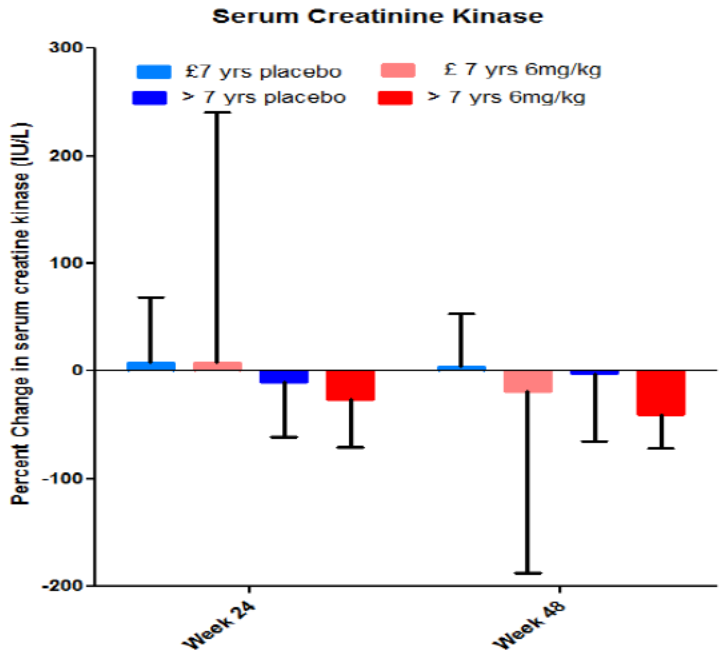
Figure 19 Change from baseline serum CK in subjects with or without injection site reactions



Source: Dr. Bhattaram

The MMRM analysis of serum CK based on age groups (≤7 years and > 7 years), showed greater reduction in CK in subjects ≤7 years, consistent with the age based analysis on 6MWD.
Since, the baseline CK is higher in the younger age group, I looked at percent reduction in these groups. At Week 48, the subjects > 7 years showed greater mean reduction in serum CK (-41%) compared to the subjects ≤7 years (-18%), opposite to what was observed when looking at adjusted mean change from baseline. There was much larger variability in the CK in subjects ≤7 years.

Figure 20 Percent change in serum creatine kinase in subjects ≤7 years and >7years



Dystrophin Measurements

Two muscle biopsies were obtained from each subject, one at Week 48, the other biopsy at either Week 8, 12, 24 or 36 from the tibialis anterior in most subjects with the exception of quadriceps in 3 subjects. No muscle biopsies were performed at baseline. Therefore the applicant analyzed the muscle biopsies for drisapersen concentration, detection on exon 51 skipping by non-quantitative RT-PCR only and the number of revertant fibers (as it could influence the amount of exon skip observed in total RNA).

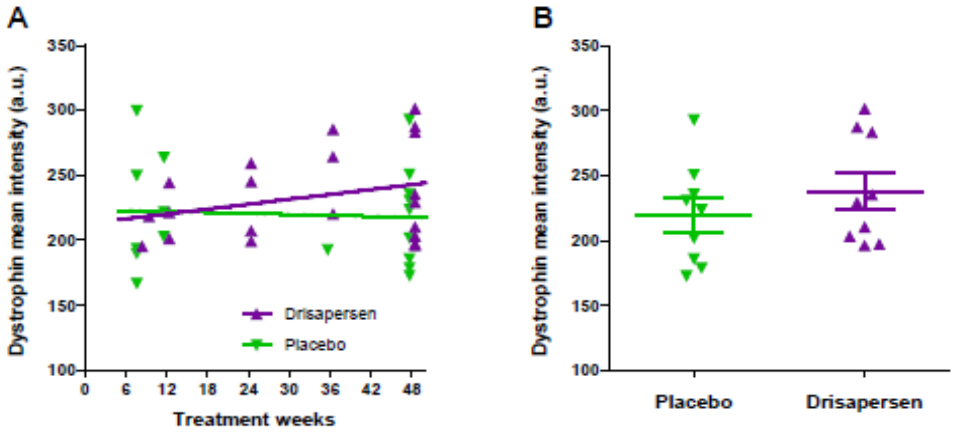
Exon 51 Skipped mRNA:
With a non-quantitative RT-PCR, skipping of exon 51 was detected in 48 (81%) subjects in the placebo group and 106 (89%) subjects in the drisapersen group at Week 48. There was a weak trend to higher intensities in the drisapersen treated group beyond 24 weeks of treatment. (Table 38).

Table 38 Exon 51 skip with non-quantitative RT-PCR

Test/ Visit	Placebo (N=61)		Drisapersen 6 mg/kg/week (N=125)	
	n	Mean (SD)	n	Mean (SD)
DMD Exon 51 skip - Integrated intensity (units)				
Week 8	20	1.75 (1.25)	26	1.25 (1.55)
Week 12	16	2.02 (1.78)	30	1.64 (1.79)
Week 24	9	1.52 (1.03)	34	2.32 (2.90)
Week 36	13	0.91 (0.56)	26	2.86 (5.18)
Week 48	56	1.43 (1.69)	114	2.49 (3.46)

Dystrophin expression by IFA:
According to the Applicant, many biopsies were not acceptable for dystrophin analysis: due to freeze damage, small size and/or relative large areas of adipose and connective tissue (indicative of advanced disease state), an insufficient number of fibers with intact membranes can be identified for a representative and reproducible result. A summary of dystrophin analysis on selected biopsies were performed by the operators that were blinded to study treatment during analysis is presented in Figure 21. The results in placebo patients show the presence of dystrophin both with IFA and WB, which is considered a result of trace dystrophin expression in many fibers and/or dystrophin expression in revertant fibers. Therefore, the applicant concluded that in the absence of pre-treatment biopsies, the IFA results would not provide relevant information in this study.

Figure 21 Dystrophin mean intensities on selected biopsies



Reviewer's Comment: The numbers of subjects were few at each time point. There was a trend of increased dystrophin intensity with a large inter-subject variability in the drisapersen group.

OBP Reviewer Dr. Rao's comments:

> **The applicant reports several problems with the quality of the biopsy samples. They state that repeated freeze-thaws of the tissue samples being shipped from multiple international sites in an aluminum tube container to a central re-distributing laboratory for analysis led to rejection of a large number of samples with freezing-related artifacts that were deemed unsuitable for IFA or WB. The absence of pre-treatment samples from the same patients probably renders any treatment-related conclusions questionable.**

MRI:
According to the Applicant, MRI data were only acquired in a small number of subjects and data were not analyzed due to technology issues at acquisition.

Applicant's discussion on lack of response in this study:

The applicant attributes the following factors to have led to a less favorable outcome in this Phase 3 study:

- **Demographic and baseline population makeup** – Subjects in DMD114044 had, on average, more functional impairment than subjects in the Phase II studies (as measured by baseline 6MWD). Also, unlike the Phase II trials, DMD114044 did not include a baseline requirement for performance on the rise from floor assessment. This change led to further enrolment of older, more severely progressed subjects in DMD114044, most of whom would not have met the criteria for enrolment in the Phase II studies. According to the applicant, these patients would have had fewer intact muscle cells where increased dystrophin levels due to exon skipping would have an impact. Pre-specified subgroup analyses of the DMD114044 data show that subjects ≤7 years performed similarly at Week 48 to subjects in the Phase II studies, with a 21 meter treatment effect in favor of 6 mg/kg/week drisapersen (not statistically significant). Subjects >7 years in DMD114044 showed a small numerically favorable treatment effect (7 meters) and a large decline from baseline 6MWD performance (-76 meters), possibly indicating subjects in the decline phase of their ambulatory capacity.
- **Treatment duration-** 48 weeks not adequate to demonstrate treatment benefit in a heterogeneous population
- **Lack of a loading dose** – unlike Study DMD114117, there was no loading dose in DMD114044. As a result, subjects likely took longer to achieve steady state for drug effect. This could be important in an already more progressed population.
- **Multiple centers** – because of the size of the study, DMD114044 required more study sites in more countries (44 sites in 19 countries) than were employed in the Phase II studies, including some sites that were not specialized in DMD management. This global reach is likely to have led to increased variability in standard of care in areas such as steroid usage and frequency of formal physiotherapy. A post hoc analysis of DMD114044 sites previously participating in study DMD114117 showed a difference of 62 m (p=0.06) in change from baseline 6MWD at Week 48 between drisapersen 6 mg/kg/week (-47m; n=17) and placebo (–109m; n=9) suggesting that experience in management of DMD patients and in conducting assessments in the context of a clinical trial, may help to decrease variability and enable detection of a treatment effect.

Reviewer's analysis/discussion:

The only strength of this study was:

- **A favorable effect of serum creatine kinase at Week 48 (p=<0.001). No apparent relationship was observed between reduction in CK from baseline and 6MWD response. There is a 30-40% reduction in CK across studies.**
- **There were some differences observed in the patient population that could have an unfavorable prognosis in the drisapersen group in this study, although it is unlikely that these differences could account for some modest differences in the outcome in a large study. In a large study these differences in baseline characteristics are difficult to interpret.**
    - **There were 17% subjects >11 years in the drisapersen group compared to 11% in the placebo group.**

  - **There were 18% of subjects with baseline 6MWD <150m and in between 250-300m in the drisapersen group compared to 12% in the placebo group.**
  - **There were 49% subjects with baseline 6MWD >350 m in the drisapersen group compared to 54% in the placebo group.**
- **The study design was identical to the phase 2 studies, with the exception of no restriction on the ability to rise from floor. Hence, subjects >7 seconds were also enrolled in this study. In a post-hoc analysis in subjects with Rise from Floor <7seconds, the treatment difference of 5 m was observed, which was smaller than in the DMD114044 population as a whole (10 m). The applicant indicates that the greater range of rise from floor values at baseline was not the primary reason for the differing results.**
- **In a post-hoc analysis, the applicant states there was a treatment difference of 62m in favor of drisapersen in study sites that participated in prior drisapersen studies, and might have been more experienced at collecting data. However, I assessed the quality of data for the primary and key secondary endpoints across studies and centers and there did not appear to be any meaningful or systematic differences in the values or trajectories between centers that would suggest differences in the way the data was collected (See Appendix C). The sponsor's analysis therefore does not appear reasonable. Furthermore, the remaining sample size of this entirely post-hoc analysis is so small, 9 subjects in the placebo group and 17 in the drisapersen group, that it could have readily arisen by chance alone.**

The weaknesses of this study are:

- **The primary endpoint (change from baseline in 6MWD at Week 48) did not show a statistically significant treatment difference from placebo, although the study was a well-designed and executed study with good statistical power to detect a small effect.**
- **Percent change from baseline in CK based on age group is not consistent with age group effect on treatment response on 6MWD, but so was reduction in CK not consistent with treatment effect in the primary analysis. (i.e. treatment difference with 6MWD negative, treatment difference with CK positive)**
- **No consistent trends in favor of drisapersen were observed for any key or other secondary endpoints.**
- **There could have been partial unblinding due to differences in injection site reactions between the drisapersen (78%) and placebo groups (16%) leading to lean in 6MWD in favor of drisapersen. Although, the impact of potential unblinding is not as apparent in this study as though directionally favorable, the effect size was small. Nevertheless, a small numerical difference between treatments could be due to unblinding.**
- **There was a weak trend of higher intensity of exon 51 skipping.**

6.4. Study DMD114349 (Open label extension study)

6.4.1. Study Design

Overview and Objective

This study was designed to assess the long-term safety, efficacy, and tolerability of drisapersen for at least 104 weeks in subjects with DMD who previously participated in either feeder study (DMD114117 or DMD114044). The study was terminated early because results of Study DMD114044 showed that the primary efficacy endpoint was not achieved.
Study Dates: 19 September 2011 to 17 March 2014 (termination) (no dosing occurred after 20 September 2013)
Study Centers: 58 centers in 24 countries: Argentina, Australia, Belgium,
Brazil, Bulgaria, Canada, Chile, Czech Republic, Denmark, France, Germany, Hungary, Israel, Italy, Japan, Republic of Korea, The Netherlands, Norway, Poland, Russian Federation, Spain, Taiwan, Turkey, and United Kingdom.

Trial Design

This was a Phase III, multicenter, open-label, uncontrolled extension study in subjects with DMD who had completed the double-blind treatment phase in DMD114117 or DMD114044. Eligible subjects entered into a 4-week Run-in period of the study. No assessments were conducted and no drug was administered during this Run-in period.
Study Population: 6- to 17-year-old (median of 9 years males were enrolled. Subjects entering this study had mean times since first symptoms, diagnosis, and first corticosteroid use of 80.4, 66.1, and 43.9 months, respectively. The corticosteroid regimen given during the feeder studies (DMD114117 or DMD114044) was continuous for 80% of the subjects and intermittent for 20%.
Dosing Regimen: The primary dosing arm for all subjects was 6 mg/kg/week continuous dosing for at least 104 weeks, but subjects had the option of intermittent dosing (6 mg/kg/week for 8 weeks and 4 weeks off drug) based on safety and tolerability issues. At any point during the study, subjects could discontinue active treatment and move to the natural history observation arm for the duration of the study or until Early Withdrawal.
Primary endpoint: Change from baseline in muscle function using the 6MWD test assessed at Week 104. (Note: Baseline efficacy assessments were only required for those subjects who had withdrawn early from the feeder studies and who did not have these assessments performed within the previous 3 calendar months, for other last assessment from feeder studies were used as baseline).
Secondary endpoints: same as feeder studies.
Muscle Biopsy for dystrophin expression: Only subjects who showed an unexpected decrease in efficacy required a muscle biopsy, defined as two consecutive 20% decreases in 6MWD after Week 24 in those subjects previously demonstrating improvement or maintenance of 6MWD (unless an alternative explanation (e.g., fall)
MRI: MRI was to be conducted in those subjects where it was obtained in Study DMD114044

Statistical Analysis Plan

No formal interim analysis, but the first data-cut was planned for 05 June 2013.
The primary population for evaluation of efficacy parameters was the Modified ITT population, defined as all subjects enrolled in the study that received at least 1 dose of investigational product, or entered the natural history arm at the start of the study and as such did not take any investigational product, and had at least one post-baseline efficacy assessment. A Modified Ambulant ITT population, defined

as above, but only in the ambulant population was used for analysis using pre-specified MMRM model with a 5% significance level was used for 6MWD, NSAA and timed function tests. An analysis pooling all the subjects from the two studies was uninterpretable; hence the applicant conducted post-hoc analyses based on parent studies.

Data Quality and Integrity: Sponsor's Assurance

This study was conducted in accordance with ICH GCP and all applicable subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2008. Management of clinical data was performed in accordance with applicable GSK standards. The study was monitored in accordance with ICH E6.

6.4.2. Study Results

Patient Disposition

A total of 233 subjects were enrolled. 228 subjects were assigned to continuous treatment with drisapersen 6 mg/kg/week, 4 subjects were assigned to intermittent treatment with drisapersen 6 mg/kg (12 week cycles of drisapersen 6 mg/kg/week for 8 weeks followed by 4 weeks of no dosing), and 1 subject was assigned to the natural history arm (no treatment). Of the 228 subjects assigned to continuous treatment with drisapersen 6 mg/kg/week at the start of the long-term extension study, 8 switched to intermittent treatment, 15 subjects switched to the natural history arm, and 1 of the subjects who initially switched to intermittent treatment switched to the natural history arm due to an AE. The final numbers in each arm after switching regimens during study were: Continuous N=205, Continuous to Intermittent N=7, Continuous to Intermittent to natural History N=1, Continuous to Natural History N=15, Intermittent N=4, Natural History N=1. The number of subjects that withdrew during the study and the reason is shown in Table 39. The rest of the subject's attrition was due to termination of the study.

Table 39 Subjects withdrawn

	Number of subjects
Subjects Withdrawn	17
Reason	
AE	3
Lack of efficacy	2
Protocol Deviation	1
Withdrew Consent	11

Note: only 1 subject who withdrew was from Study DMD114117

Subjects were treated with 6 mg/kg drisapersen continuously over a mean total duration of 353 days; 74%, 57%, and 24% of the subjects received investigational product for ≥24 weeks, ≥48 weeks, and ≤72 weeks, respectively. Due to the small numbers of subjects in the drisapersen intermittent treatment group or the natural history arm at the time of early study termination, applicant's discussion focuses

on the drisapersen continuous treatment group through 72 weeks (N=55). The cumulative exposure of each regimen is given in Table 40.

Table 40 Summary of cumulative exposure

	6 mg/kg Drisapersen Continuous	6 mg/kg Drisapersen Intermittent	6 mg/kg Drisapersen (Combined)	Natural History
Cumulative Duration of Exposure (weeks), n (%)				
n	228	12	232	17
0 weeks	0	2 (17)	0	0
>0 weeks	228 (100)	10 (83)	232 (100)	17 (100)
≥6 weeks	226 (>99)	9 (75)	229 (99)	15 (88)
≥12 weeks	201 (88)	8 (67)	205 (88)	13 (76)
≥18 weeks	178 (78)	7 (58)	181 (78)	11 (65)
≥24 weeks	168 (74)	5 (42)	171 (74)	9 (53)
≥48 weeks	131 (57)	3 (25)	136 (59)	3 (18)
≥72 weeks	55 (24)	0	60 (26)	0
≥104 weeks	0	0	0	0

Source: NDA 206, 031 Study Report DMD114379

Protocol Violations/Deviations

Protocol deviations were reported by the site for 230 (99%) subjects overall, mostly related to study procedures/assessments not performed on the exact day, but reviewing the data they were mostly within 1 week of the scheduled visit. A total of 23% of the subjects eitherhad an extra dose, did not get a dose, got a wrong dose or dose was given at an incorrect time.

Table of Demographic Characteristics

The study population consisted of 6- to 17-year-old (median of 9 years), predominantly White (78%), non-Hispanic (86%) males. Baseline age characteristics are shown in Table 41.

Table 41 Baseline Age

Demographic Characteristic	6 mg/kg Drisapersen Continuous (N=205)	6 mg/kg Drisapersen Intermittent (N=11)	Natural History (N=17)	Total (N=233)
Age (years)				
Mean (SD)	8.9 (2.12)	9.9 (1.73)	8.7 (1.69)	9.0 (2.14)
Median	9.0	9.5	9.0	9.0
Min, Max	6, 17	8, 14	6, 12	6, 17

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

81% of the subjects were more than 80% compliant.

Efficacy Results - Primary Endpoint

Applicant's Analysis:
The applicant considered the results pooling subjects from the two parent studies uninterpretable, because the parent studies showed different results and the population was more progressed in Study DMD114044, an analysis based on each parent study was considered appropriate by the applicant. The applicant considers subjects from study DMD114117 more functional population and subjects in Study DMD114044 as a more progressed population. The change from original baseline in 6MWD from parent studies is shown in Table 42 and Table 43.

Table 42 Change from original baseline in 6MWD (m) by parent study (Study DMD 114117)

Treatment in parent study (DMD114117)	Placebo	Drisapersen 6 mg/kg/week	
Treatment in DMD114349	Drisapersen 6 mg/kg weekly or intermittent	Drisapersen 6 mg/kg/week	Drisapersen 6 mg/kg weekly or intermittent
Original baseline, n Mean (SD)	18 403 (45)	18 428(70)	18 428 (70)
Change to Study 349 Week 48, n Mean (SD)	14 –55 (78)	16 1.24 (69)	17 –5 (68)
Change to Study 349 Week 72, n Mean (SD)	11 –89 (126)	12 -33 (71)	13 –39 (71)

Source ISE Table 10.1.3

Table 43 Change from original baseline in 6MWD (m) by parent study (Study DMD 114044)

Treatment in parent study	Placebo	Drisapersen 6 mg/kg/week	
Treatment in DMD114349	Drisapersen 6 mg/kg weekly or intermittent	Drisapersen 6 mg/kg/week	Drisapersen 6 mg/kg weekly or intermittent

Original baseline, n Mean (SD)	60 348 (93)	116 346 (92)	119 343 (94)
Change to Study 349 Week 48, n Mean (SD)	37 –123 (135)	61 –92 (130)	61 –92 (130)
Change to Study 349 Week 72, n Mean (SD)	25 –173 (132)	35 –108 (134)	37 –106 (132)

Source ISE Table 10.1.3

According to the applicant, subjects who received drisapersen in both the parent study were combined, the subjects on drisapersen continuous regimen in both parent and the extension study had a smaller decline in 6MWD (-89 m) than those who received placebo in the parent study followed by drisapersen in the extension study (-142 m) at Week 72 (overall Week 120). The treatment difference in the two groups (continuous and delayed start was, 31m at Week 96 (from study baseline) and 59m at Week 120.

Based on these results, the applicant believes that this reinforces the notion that subjects who are treated younger (and presumably prior to the onset of more serious functional impairment) will get a greater benefit of treatment with drisapersen in the long-term. At the time of study termination, 21 (10 %) subjects in the continuous treatment arm lost ambulation. Four subjects required respiratory support during sleep.

Efficacy Results - Secondary and other relevant endpoints:

Timed Tests, Muscle strength and NSAA: Small changes from baseline were observed on secondary endpoints (e.g., muscle strength, timed muscle function tests [rise from floor, 10-meter walk/run, 4-stair climb (ascent/descent)], NSAA total score) in both the delayed placebo and drisapersen arms in both studies at different visits. The applicant only discusses the results in terms of the continuous regimen. Subject on the intermittent regimen when switched to continuous regimen continued to show larger decline, consistent with the greater impairment in this group at baseline.
Pulmonary Function tests: No clinically meaningful change was seen in any pulmonary function test.
PedsQL, Health Utilities Index, CGI-I, Functional Outcome Assessment: No meaningful differences in the continuous drisapersen arm and the delayed drisapersen arm
Serum CK: CK showed a decline over 72 weeks, but was very variable.
Dystrophin and MRI: No subjects demonstrated an unexpected decrease in efficacy that required a muscle biopsy to quantitate dystrophin expression. No MRI or dystrophin expression data has been provided from this study.

Reviewer's Comment: The durability of response is uninterpretable from this study as not all subjects completed the study.

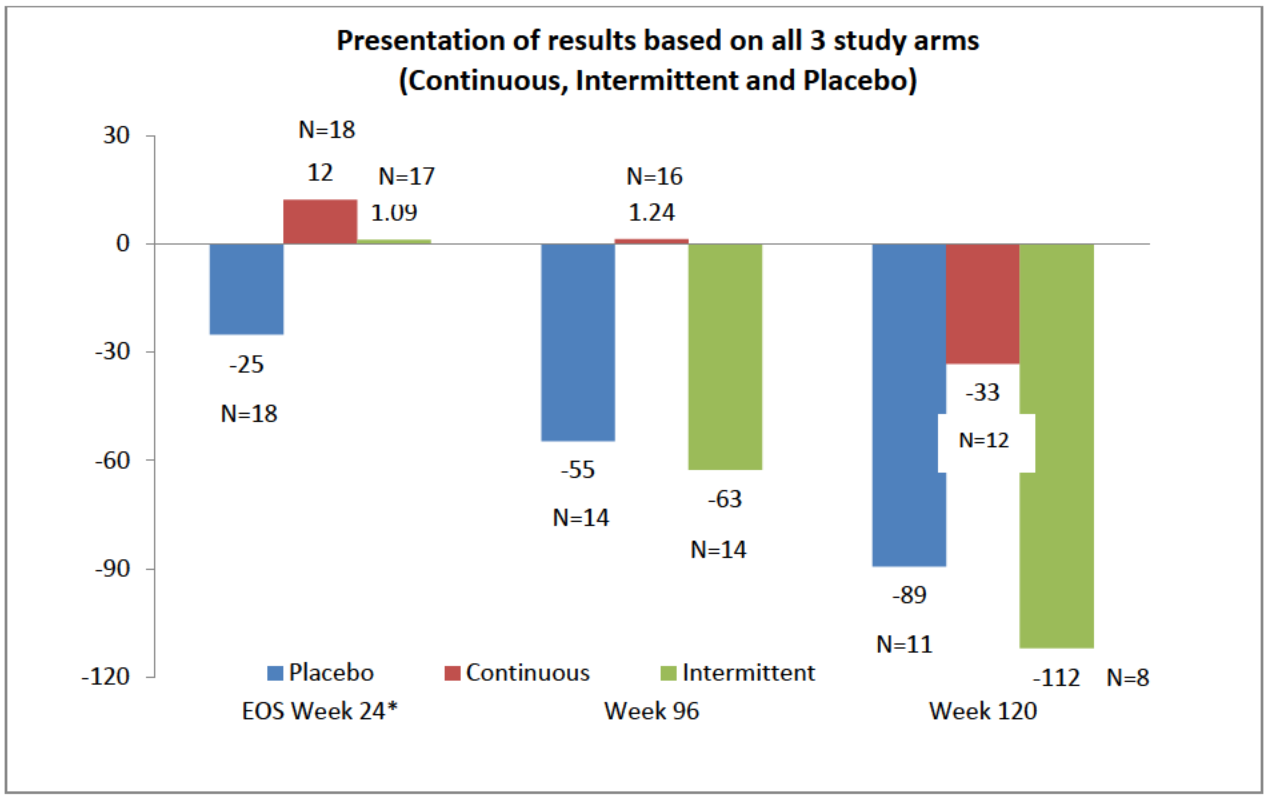
Reviewer's Comments/Discussion:

The dropout of subjects during the study and the lack of control make this study uninterpretable, even if the analyses are on parent studies. A total of 26%, 43% and 76% of the subjects dropped out from the study at 24 weeks, 48 weeks and 72 weeks due to AE or termination of the study.

The Applicant has discussed the open label extension results based on the parent studies. For Study DMD114117, the results have been discussed only for the continuous 6 mg/kg/week drisapersen arm and the placebo arm switched to the 6mg/kg/week regimen. The parent study DMD114117 was a three arm study with 18 subjects each on intermittent and continuous drisapersen 6mg/kg regimen. The subjects that were in intermittent regimen in the parent study, when switched to continuous 6mg/kg/week regimen under Study DMD114349, continued to decline (Figure 22). These subjects appeared to have more functional impairment compared to the continuous treatment arm at baseline of the parent study as also stated by the applicant in the ISE and their probable reason that the intermittent group did not show treatment difference from placebo. The applicant has not explained the evidence supporting efficacy in context of the deterioration seen in these subjects when switched to continuous regimen from the intermittent regimen in the parent study. While these data are not completely interpretable because not all subjects completed their assigned treatments during the study, but do suggest the subjects appear to follow their course of progression. The disease trajectories appeared to be different in the three treatment arms at the start of the study.

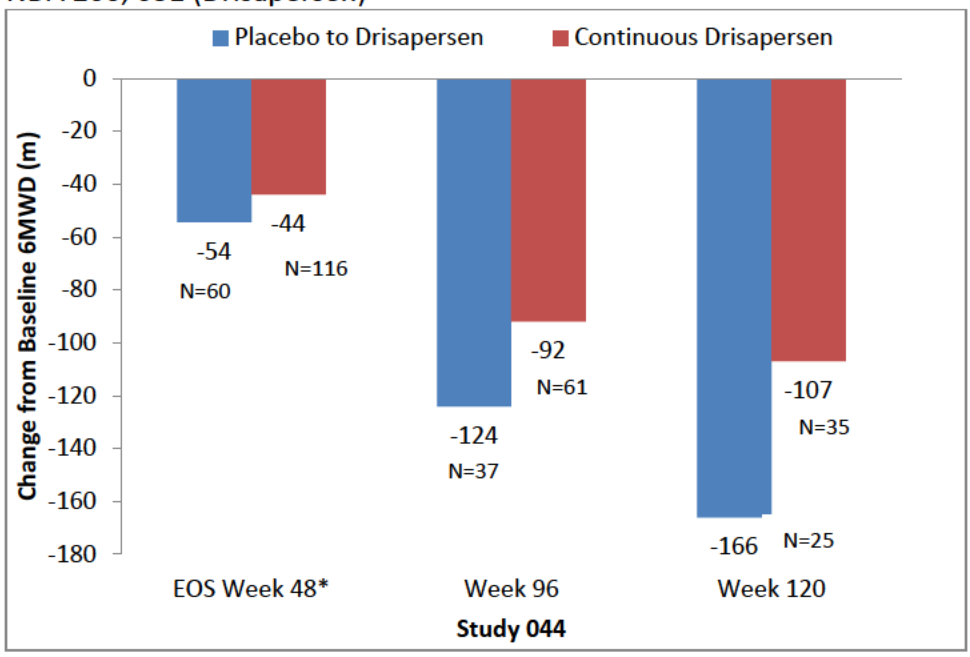
Based on these results of extension of Study DMD114117, the applicant believes that this reinforces the notion that subjects who are treated younger (and presumably prior to the onset of more serious functional impairment) will get a greater benefit in the long-term of treatment with drisapersen. While it may seem logical that it may be pharmacologically easier to restore dystrophin before much muscle damage occurs, and hence benefit may be discernable when treated young, there is no clear evidence supporting this hypothesis. Published natural history data suggest that some subject can have better prognosis than other based on baseline 6MWD, age and genetic disposition (LTBP4 genotype predicts age of ambulatory loss in DMD). In addition, experts in the area have also shown that higher baseline function is almost always associated with slower long-term decline in DMD. (McDonald: http://www.treatnmd.eu/downloads/file/meetings/2013/workshop/Session1/McDonald_NH.pdf

Figure 22: Adjusted mean change from baseline 6MWD in the open label extension of Study DMD114117 (all three arms presented)



At weeks 96 and 120, treated subjects from parent Study DMD114044 had larger decline in the extension phase (Figure 23**). This is consistent with a more impaired population. The applicant also asserts that that treatment benefit is slower to emerge in subjects with advanced age. While this could be true, the drop out of subjects during the study (N's shown in the figure), preclude reliable conclusions from this study. Therefore, there is no convincing evidence suggesting longer treatment would be needed to show treatment benefit in subjects with advanced age and more functionally impaired subjects.**

Figure 23 Adjusted mean change from baseline 6MWD in the open label extension of Study DMD114044



6.5. Study DMD114673 (Open Label Extension Study)

6.5.1. Study Design

Overview and Objective

This was an open label long-term extension of Study PRO051-02 (a 5 week dose escalation study with 0.5, 2, 4 and 6 mg/kg doses) in patients with Duchenne muscular dystrophy. The Applicant has used this as a historically controlled Study.

Study Date: 30 July 2009 (start of Continued Treatment Phase) to 26 Mar 2013 (completion of 188 week), 25-Jun 2013 (completion of IV sub-study)
Study Centers: 2 centers (Belgium and Sweden)

Trial Design

All subjects from Study DMDPRO51-02 were moved to a Continued Treatment Phase with 6 mg/kg/week dose. The applicant's intension is to continue treatment for 216 week. Data up to 188 week has been included in this NDA. Baseline assessments were conducted again prior to the first dose in the Continued Treatment Phase at Visit 13. Safety, efficacy and pharmacokinetic assessments were conducted at regular intervals throughout the Continued Treatment phase. Glucocorticoid use was to be kept constant during the study unless medical reasons dictated otherwise.
Inclusion Criteria:

- Boys aged between 5 and 16 years
- Not ventilator dependent
- Life expectancy of at least six months

Exclusion Criteria:

- Any subject who did not complete the initial Study Period of PRO051-CLIN-02
- Aberrant RNA splicing and/or aberrant response to drisapersen, detected by in vitro drisapersen assay during screening.
- Known presence of dystrophin in ≥5% of fibers in a pre-study diagnostic muscle biopsy
- Severe muscle abnormalities defined as increased signal intensity in >50% of the tibialis anterior muscle at MRI
- FEV1 and/or FVC <60% of predicted, history of liver or renal disease, severe cardiac myopathy

Dosing Regimen:

- Between PRO051-02 and DMD114673 subjects received no drisapersen treatment for 6-15 months.
- From Visit 13 to Visit 85 (Study Week 72), all subjects received a weekly s.c. dose of 6 mg/kg.
- Starting Visits 86 to 93 (Study week 73-80), all subjects had a 8 week wash-out period due to the emerging safety data from other studies. It was anticipated that the washout would not compromise efficacy due to the predicted retention of drug in muscle and the known long half-life of dystrophin.
- At Visit 94 (Week 81) subjects restarted drisapersen on a 12 week cycle intermittent regimen (8 weeks treatment of 6 mg/kg followed by 4 weeks off-treatment). Based on PK/PD, the intermittent regimen, the dystrophin levels were predicted to be 70% of the level prior to wash-out and 80% at the end of the 8 week treatment period. This measure was taken to minimize the hepatotoxicity and nephrotoxicity.
  If a perceived continuous decline in efficacy was observed and where safety and tolerability was acceptable, subjects was given the option to return to continuous regimen. Treatment is currently ongoing in all subjects according to the intermittent dosing schedule and no subjects have reverted to continuous weekly dosing up to Visit 201 (Week 188).

A weight cap on dosing was implemented:

- subjects with body weight <50 kg continued to be dosed with 6 mg/kg drisapersen;
- subjects with body weight ≥50 kg received a fixed maximal dose of 300 mg drisapersen.

Injection was preferred in the abdominal subcutis but alternate sites were allowed. Injections had to be separated by at least 4 inches, if two or more injections were required at a given time.

Study Endpoints

- 6MWD
- Timed Function Tests (10m walk/run, Rise from Floor, Stair Climb)
- Muscle Strength by handheld myometry
- Pulmonary Function (FVC, FEV1, MEP, MIP, PC and PCF)
- Muscle Biopsy at Visit 37 (week 24) and Visit 65 (Week 52, optional), Visit 81, optional
    - mRNA production
    - Dystrophin Expression
- Parent Questionnaire to capture:
    - loss of any skills or daily activities,
    - improvements in daily activities,

- development of new skills

Statistical Analysis Plan

Study was analyzed by only descriptive statistics.

Data Quality and Integrity: Sponsor's Assurance

The study was conducted according to ICH GCP guidelines for assuring proper study conduct with regard to protocol adherence and validity of the data recorded on the CRFs. The study was monitored in accordance with ICH E6.

6.5.2. Study Results

Patient Disposition

All 12 subjects who participated in the initial 5 week Study DMD PRO051-02 were subsequently enrolled into the Continued Treatment phase and the study is ongoing.

Protocol Violations/Deviations

There were no major protocol deviations; hence ITT and PP population are the same. All subjects had missed one or more doses up to Visit 202. 8 subjects had ≤ 10 missed doses. The number of missed doses in the 4 other subjects were 11, 15, 25 and 32.

Table of Demographic Characteristics

At the end of Visit 190, subjects are between the ages 9-18 years

	N	Mean	Min	Max
Age at Screening	12	9	5	13
Age at Visit 190	12	13	9	18

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The time interval between the two baseline visits was approximately 6 to 15 months. At entry, subjects were classified as either “Stable” or “Declining” based on the investigators’ clinical examinations combined with judgments from the subjects’ parents, home physiotherapists or other relevant individuals (e.g. teachers). Subjects in the ‘decline’ group were on average older, taller and heavier than subjects in the ‘stable’ group. The subjects’ baseline classification is presented in Table 44. The applicant notes that the median walking distance (N=11) had reduced by ~20 m in the time between their inclusion in the initial Study Period and Baseline (Visit 13) in the Continued Treatment Phase.

Table 44 Baseline Status of Subjects

Demographics at Visit 13 by baseline status	N	Mean	SD	Median	Min	Max
Stable						
Age (years)	7	9	2	9	6	11
Body height (cm)	7	116	9	118	97	124
Body weight (kg)	7	24	4	25	15	28
Body Mass Index (kg/m^2)	7	18	2	18	15	21
Decline						
Age (years)	5	12	2	12	10	14
Body height (cm)	5	135	6	136	125	141
Body weight (kg)	5	39	13	37	28	61
Body Mass Index (kg/m^2)	5	21	5	18	18	31

*Stable subjects included Subjects 101, 102, 104, 105, 202, 206 and 207.
*Declining subjects included Subjects 103, 106, 107, 201 and 205 (Subject 103 had the maximum number (N=32) of missed dose, subject 201 was non ambulant).

<u>Reviewer's Comment:</u> The "Stable" and "Decline" groups differed in their baseline 6MWD and Rise from Floor Time as shown below. The "Stable" subjects were atypical in the entire development program, with very Rise From Floor Time.

Baseline	Mean (SD) 6MWD (m)	Mean (SD) Rise From Floor (s)
Stable	435 (108)	2.4 (0.36)
Decline	217 (96)	8.5 (1.85)

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

All subjects received corticosteroids during the Continued Treatment phase and no changes in dosing regimen, other than for routine weight adjustment, except Subject 207 who had his steroid treatment changed to an intermittent dosing regimen.

All subjects missed at least one dose. None of the subjects were dosed at Visits 86 to 93 (washout) and Visits 102 to 105, 114 to 117, 126 to 129, 138 to 141, 150 to 153, 162 to 165, 174 to 177, 186 to 189 and 198 to 201 (off-drug periods). These were not counted as missing dose. Overall compliance was considered to be 92%

Efficacy Results - Primary Endpoint

<u>Applicant's results and Conclusions:</u>

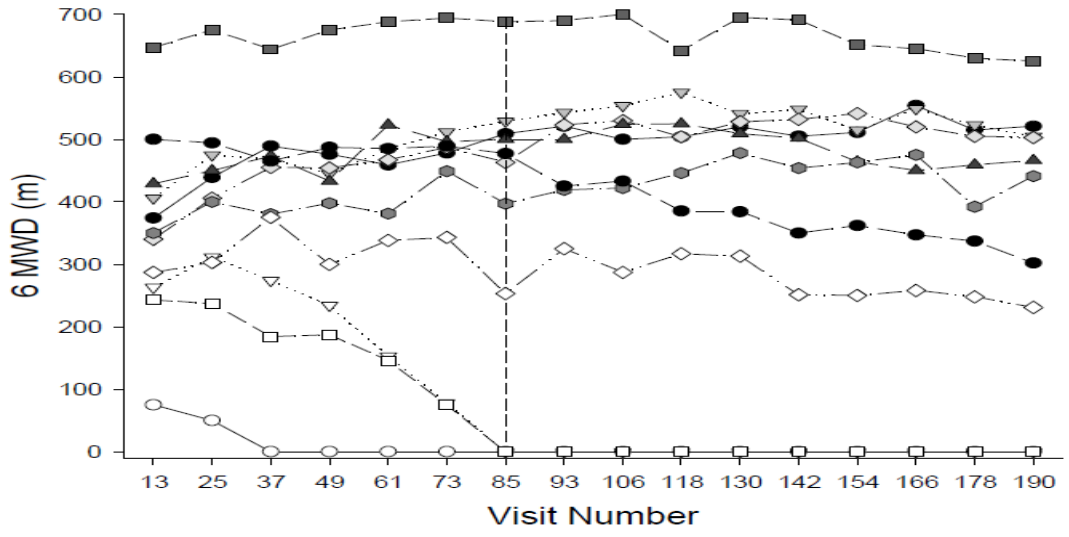
<u>6MWD:</u>

- 10 subjects completed the 6MWD, two subjects (103 and 201) lost ambulation at Visit 37 and 85 respectively.

- 7 subjects were classified as "stable" and 5 as "decliners" at entry to the study, based on baseline 6MWD and medical judgment.
  - Amongst the "stable" subjects, one subject (#207), continued to decline (500 m to 302 m). The mean change from baseline for the 6MWD at Week 177 in the stable group showed an improvement of 45m (range -198 to +163m). In general improvement appears to be maintained until Visit 142 (Week 129) (Table 45)
  - Amongst the 5 "decliners",
    - 2 subject became non ambulant.
    - The remaining 3 subjects had continued to decline to the extent that they could not attempt the 6MWD at later visits.
    - A reduction in those in the decline group (excluding Subject #103 who couldn't complete the assessment at entry) of -187m (range -263 to -56m) (Table 45).
- In the 10 subjects who were able to complete the 6MWD at Visit 13 (study baseline), the median change in 6MWD from Visit 13 to Visit 190 (Week 177) was 8 m (mean change: –25m).
- Five of the 10 subjects who could complete the 6MWD at baseline (Visit 13), could still walk further (range 37 to 163 m) at Week 177 with 2 subjects still being able to walk over 140 meters further at Visit 190 (Week 177) than they could at baseline (Visit 13).
- Introduction of an intermittent dosing regimen following Week 72 (Visit 85) did not appear to adversely affect efficacy parameters.

The absolute change from baseline in 6MWD is shown in Figure 24

Figure 24 Absolute 6MWD over 190 Weeks



Source: Study DMD114673 report, page 65, Note: Stable subjects have filled symbols; 'Decline' subjects have open symbols. Vertical line denotes start of intermittent dosing regimen at Visit 85

Table 45 6MWD – Only Subjects Who Completed Test at Visit 13 (Split by Baseline Status)

Visit	Stable Subjects					Declining Subjects				
	N	Change from Baseline in Continued Treatment Phase (Visit 13) (m)		Change from Baseline in Main Study (m)		N	Change from Baseline in Continued Treatment Phase (m) (Visit 13) (m)		Change from Baseline in Main Study	
		Mean (SD)	Median	Mean (SD)	Median		Mean (SD)	Median	Mean (SD)	Median
13	7	-	-	5.7 (53.97)	-5.0	3	-	-	-73.0 (15.52)	-74.0
25	7	41.9 (28.40)	50.0	47.6 (42.48)	39.0	3	19.7 (27.68)	16.0	-53.3 (24.95)	-63.0
37	7	46.9 (56.27)	44.0	52.6 (40.76)	42.0	3	13.3 (73.53)	11.0	-59.7 (58.07)	-63.0
49	7	46.0 (47.23)	39.0	51.7 (47.14)	28.0	3	-24.0 (34.77)	-29.0	-97.0 (19.70)	-103.0
61	7	63.1 (47.24)	79.0	68.9 (55.58)	59.0	3	-52.0 (89.44)	-97.0	-125.0 (77.67)	-154.0
73	7	79.9 (51.06)	99.0	85.6 (49.12)	86.0	3	-99.0 (134.50)	-168.0	-172.0 (122.43)	-225.0
85	7	73.9 (57.39)	71.0	79.6 (47.13)	87.0	3	-180.0 (126.84)	-243.0	-253.0 (114.95)	-300.0
93	7	82.1 (85.55)	71.0	87.9 (71.27)	87.0	3	-156.0 (168.31)	-243.0	-229.0 (156.12)	-300.0
106	7	88.1 (82.67)	95.0	93.9 (74.10)	111.0	3	-168.7 (146.41)	-243.0	-241.7 (134.36)	-300.0
118	7	76.4 (102.59)	96.0	82.1 (81.09)	97.0	3	-158.7 (163.70)	-243.0	-231.7 (151.53)	-300.0
130	7	87.0 (100.37)	128.0	92.7 (85.82)	115.0	3	-160.0 (161.39)	-243.0	-233.0 (149.24)	-300.0
142	7	76.6 (110.85)	104.0	82.3 (97.91)	93.0	3	-180.7 (125.68)	-243.0	-253.7 (113.81)	-300.0
154	7	65.9 (110.86)	109.0	71.6 (91.22)	89.0	3	-181.0 (125.11)	-243.0	-254.0 (113.24)	-300.0
166	7	70.6 (122.38)	125.0	76.3 (95.97)	106.0	3	-178.3 (129.71)	-243.0	-251.3 (117.80)	-300.0
178	7	45.0 (112.65)	42.0	50.7 (90.33)	67.0	3	-181.7 (123.96)	-243.0	-254.7 (112.10)	-300.0
190	7	45.3 (124.47)	91.0	51.0 (101.24)	79.0	3	-187.3 (114.18)	-243.0	-260.3 (102.43)	-300.0

Source: Study DMD114673 report, page 68

Note: Treatment was halted from Visit 86-93, after which subjects were on intermittent regimen (shown as grey shaded area)

Reviewer's Comment: **There is a wide range of change in 6MWD for all subjects (-263 to 163m)**

Efficacy Results - Secondary and other relevant endpoints

Timed Tests:

Subjects in the stable group were all able to complete the tests rapidly (<5 secs), compared to the subjects in the declining group in which the ability to complete the tests continued to diminish. The ability to rise from the floor was the first of these functions to deteriorate. The changes in timed tests were small Table 46.

Table 46 Timed Tests – Change from continued treatment phase baseline

Visit	N	10m Walk/run (sec)		Rising from floor (sec)		Stair Climb (sec)	
		Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	Median
21	11[a]	0.08 (1.184)	0.14	0.50 (1.723)	0.43	-0.85 (1.791)	-0.14
25	11[a]	0.27 (0.515)	0.30	-0.20 (0.577)	-0.08	-1.07 (2.110)	-0.34
29	11[a]	0.61 (0.621)	0.53	0.06 (0.655)	0.07	-0.40 (1.603)	-0.14
33	10[a]	0.56 (0.761)	0.33	1.000 (2.632)	0.22	-0.45 (1.064)	-0.34
37	10[a,b]	0.40 (0.388)	0.30	-0.08 (0.923)	-0.06	-0.18 (1.554)	-0.04
41	10[a]	0.79 (1.133)	0.58	0.55 (0.789)	0.31	-0.61 (1.690)	-0.15
49	10[a,b]	0.51 (1.010)	0.31	0.82 (1.620)	0.24	-0.37 (1.248)	-0.21
61	10[b,c]	0.82 (1.181)	0.38	0.30 (0.656)	0.14	-0.50 (0.996)	-0.30
73	10[c]	0.94 (1.696)	0.12	1.04 (2.620)	0.20	-0.15 (0.677)	-0.21
85	9[c]	1.32 (2.446)	0.38	1.75 (4.031)	0.48	0.04 (1.201)	-0.04
93	9[c]	2.21 (5.229)	0.35	1.27 (2.472)	0.58	0.32 (0.859)	0.00
106	8[b]	0.49 (1.080)	0.12	1.75 (4.588)	0.12	0.76 (1.422)	0.24
118	8	0.72 (1.360)	0.24	3.09 (6.439)	0.35	1.34 (3.041)	-0.03
130	8[d]	0.99 (1.695)	0.28	1.06(1.976)	0.32	0.85 (2.063)	-0.12
142	8[e]	1.00 (1.360)	0.40	0.67 (0.904)	0.24	1.62 (3.469)	0.26
154	8[e]	1.29 (1.925)	0.66	0.44 (0.497)	0.44	1.73 (3.446)	0.59
166	8[e,f]	1.52 (1.789)	0.65	0.79 (0.625)	0.73	1.78 (4.061)	0.43
178	8[e]	1.91 (2.059)	0.78	1.12 (1.097)	0.78	3.48 (5.654)	1.01
190	8[e,f]	1.61 (2.039)	0.86	1.05 (0.914)	0.94	4.23 (10.382)	0.74

Source: DMD114673 Study Report

[a] N=9 for rising from floor
[b] N=9 for stair climb
[c] N=8 for rising from floor
[d] N=7 for rising from floor
[e] N=6 for rising from floor
[f] N=7 for stair climb

In order to interpret the results from all subjects, missing values were replaced by an arbitrary number of 30 seconds (timed considered to be maximum likely).

Reviewer's Comment: In the Table presented, the applicant excluded the worst performing subjects from the summary statistics at later visits, potentially biasing the results.

Muscle Strength: The data were highly variable both between and within subjects.
Pulmonary Function tests: The data were highly variable both between and within subjects. FVC (% predicted) and FEV1 (% predicted) tended to be lower in the declining subjects than the stable subjects. There was a trend in increase in absolute values over time, which the applicant presumes is related to growth over Visit 190. The applicant acknowledges that both the absolute and '% predicted' values have their limitations. The absolute values do not take into account subject growth, however the '% predicted' values use algorithms based on healthy subjects with a 'normal' correlation between age and height. There are no data on how well these correlations apply to DMD subjects whose growth may be stunted. In addition, accurate measurement of DMD subjects' height becomes more difficult if they have contractures and/or lose ambulation. When not measured directly, height may be over-estimated by measuring arm span, which in turn may lead to an apparent reduction in '% predicted' values compared to when their standing height could be measured.
Parent Questionnaire: In general, the majority of parents felt that their child's general condition, walking ability, and endurance was either the same or better than at the beginning of the Continued Treatment phase, with the exception of Visits 154-157 where the majority felt their child's general condition was worse than at the beginning of the Continued Treatment phase. The majority of parents considered their child's ability to climb stairs was the same or better than at the beginning of the Continued Treatment phase up to Visit 123, although subsequently the perception of this ability appeared to worsen through to Visit 178.

Table 47 Summary of Responses to Parent Questionnaire

Visits	N	Response	Questions: change in condition over the Continued Treatment phase			
			General condition	Walking	Taking stairs	Endurance
81-89	11	Better	4 (36%)	4 (36%)	3 (27%)	4 (36%)
		Same	5 (45%)	5 (45%)	3 (27%)	7 (64%)
		Worse	2 (18%)	2 (18%)	5 (45%)	0
109-123	12	Better	3 (25%)	3 (25%)	1 (8%)	0
		Same	5 (42%)	5 (42%)	6 (50%)	10 (83%)
		Worse	4 (33%)	4 (33%)	5 (42%)	2 (17%)
154-157	12	Better	1 (9%)	2 (17%)	1 (8%)	2 (17%)
		Same	4 (36%)	6 (50%)	4 (33%)	7 (58%)
		Worse	6 (55%)	4 (33%)	7 (58%)	3 (25%)
178	12	Better	1 (8%)	1 (8%)	1 (8%)	2 (17%)
		Same	8 (67%)	6 (50%)	3 (25%)	8 (67%)
		Worse	3 (25%)	5 (42%)	8 (67%)	2 (17%)

OBP Reviewer Dr. Rao's assessment of dystrophin expression:
Dystrophin expression by IFA:

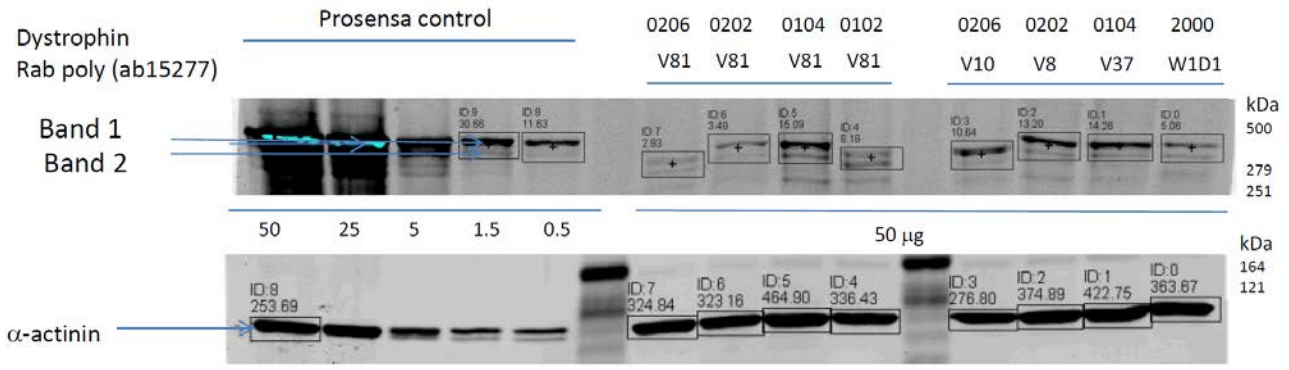
- **No reliable estimate of dystrophin expression was obtained at Week 24 of the open label**

phase due to poor muscle biopsy quality in the 12 subjects.

- **8/12 subjects had additional biopsy at Week 72. For IFA analysis, 6/8 subjects had baseline biopsies. Compared to baseline, 3/6 subjects showed slight increase (2 to 8%) in mean membrane intensity, 3/6 subjects showed a decrease (1 to 9%) at Week 72.**

<u>Dystrophin expression by WB:</u>

- **WB analysis was conducted on 8 patients. An increase of 21-46% at week 24 over previous time point was observed; however, at week 72 the same patients did not consistently show an increase.**
- **Each western blot image included a serial dilution of a healthy positive control. One representative image shown below shows the serial dilution between 0.5-50 μg of healthy control and 50 μg of DMD patient samples. Based on reviewer estimation, the observed dystrophin levels approximately ranged between 0.24 to 0.28 % (for subject 0206/V81 sample) and 1.27 to 1.47% (for subject 0104/V81 sample) of healthy control in the gels (looking at the lightest and the darkest bands on the gel). However, importantly, the α-actinin loading for these two samples do not appear to be comparable to each other, so the dystrophin expression in these two subjects cannot be reliably compared to each other**.



It appeared that most DMD samples showed a reasonable dystrophin band that was within the tested range of the positive control serial dilution shown on each gel; although, densitometric numbers are only provided for the 0.5 and 1.5 μg loaded bands for all gels suggesting saturation beyond these samples. The α-actinin bands appeared to be reasonably resolved, consistent between samples and adequately clear to allow a quantitative estimation of protein loading. Overall, for all the gel images provided, it is not possible to get an exact quantitation of the relative dystrophin due to the saturation in the dystrophin bands at higher concentrations of the healthy controls and no quantitation provided for α-actinin at the lower concentrations. The densitometric quantitations for all samples suggest a slight increase in normalized dystrophin compared to the prior time-point for some samples but a decrease for others. The modest increase appear to be below the applicant's stated threshold of >30% above baseline for a positive response.

<u>Reviewer's Comment:</u> This suggests that there is no evidence of increased dystrophin intensity over time, i.e. 72 week after the start of the open label study. The Applicant suggests that problems with the quality of the sample preclude conclusive interpretation. However, it appears that the quality of

the samples and Western blots was adequate to exclude that there was anything other than a very small increase in dystrophin expression due to treatment.

OBP Reviewer Dr. Rao's comment:

> **Upon request, the applicant clarified that, with the exception of one sample at 1.1% the dystrophin levels observed in this study were all below 1%, which is their lower limit of detection by WB.**

Persistence of Effect

No dose was given between Visits 86-93, after which subjects were switched to intermittent regimen. Change from baseline appeared to be the same in the "Stable" subjects. However, it is unclear if this is persistence of effect (see Reviewer discussion below)

Additional Analyses Conducted on the Individual Trial

Comparison to Natural History (NH):

Applicant's conclusion on natural history comparison:

- Most NH subjects had worse functional trajectory compared to matching drisapersen subjects. Three subjects were excluded from the matching analysis:
  - Subject 104 was considered atypical, had baseline 6MWD of >600m and functional capacity was maintained for 3.4 years
  - Subject 201 was non ambulant at baseline
  - Subject 103 had a single match and only one assessment from the point of matching
- Substantial gains up to 192 m from baseline were reported. Increases of this magnitude were not seen in NH controls.
- The difference in subjects that declined and NH was less easy to discern.

FDA Analysis based on natural history

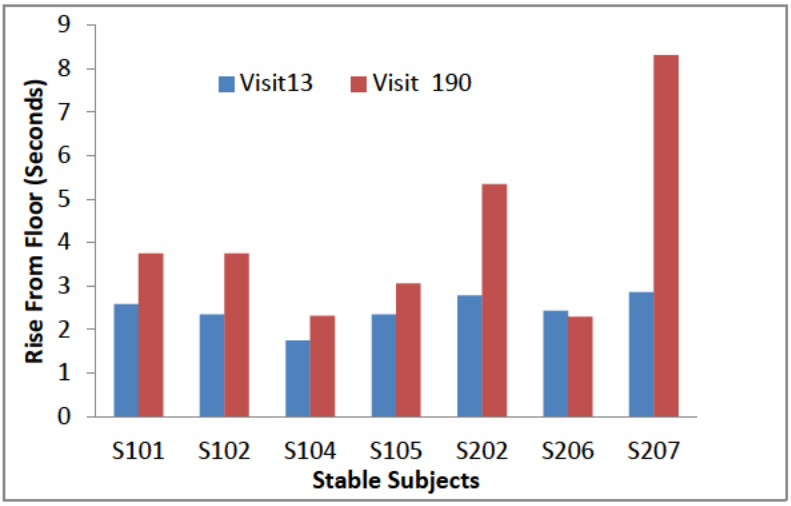
This analysis was conducted by Dr. Bhattaram (Pharmacometrics). FDA analysis suggested that there were insufficient number of patient matches (based on age, 6MWD, rise from floor and exon 51) from the natural history dataset provided to obtain reliable comparisons. Please refer to Dr. Bhattaram's review for details on the analysis.

Reviewer's Analysis and Discussion:

The "Stable" subjects (N=7) were between 5 and 10 years of age. The "Stable" subjects had Rise Time From Floor between 1.7 -2.8 seconds at study baseline (Week 13) and between 2.3-5.3 seconds at end of study at Week 190. Only one subject had a Rise from Floor Time of 8.3 seconds at Week 190. Five of these subjects had baseline 6MWD between 374-647 m and two subjects had baseline 6MWD of 340 and 350 m. (Figure 25). These subjects appear to have a milder prognosis. The mean (SD) change from baseline in the "Stable" subjects was 45 (124)m at Week 190.

The "Decline" subjects (N=3) had baseline Rise from Floor of 7.2-9.4 seconds and a maximum of 28.5 seconds at Week 118. No subject could perform the test beyond Week 118 (See Figure and Table below for the Rise from Floor Time and the baseline 6MWD in the "Stable" Subjects.

Figure 25 Rise from Floor and 6MWD in "Stable" subjects

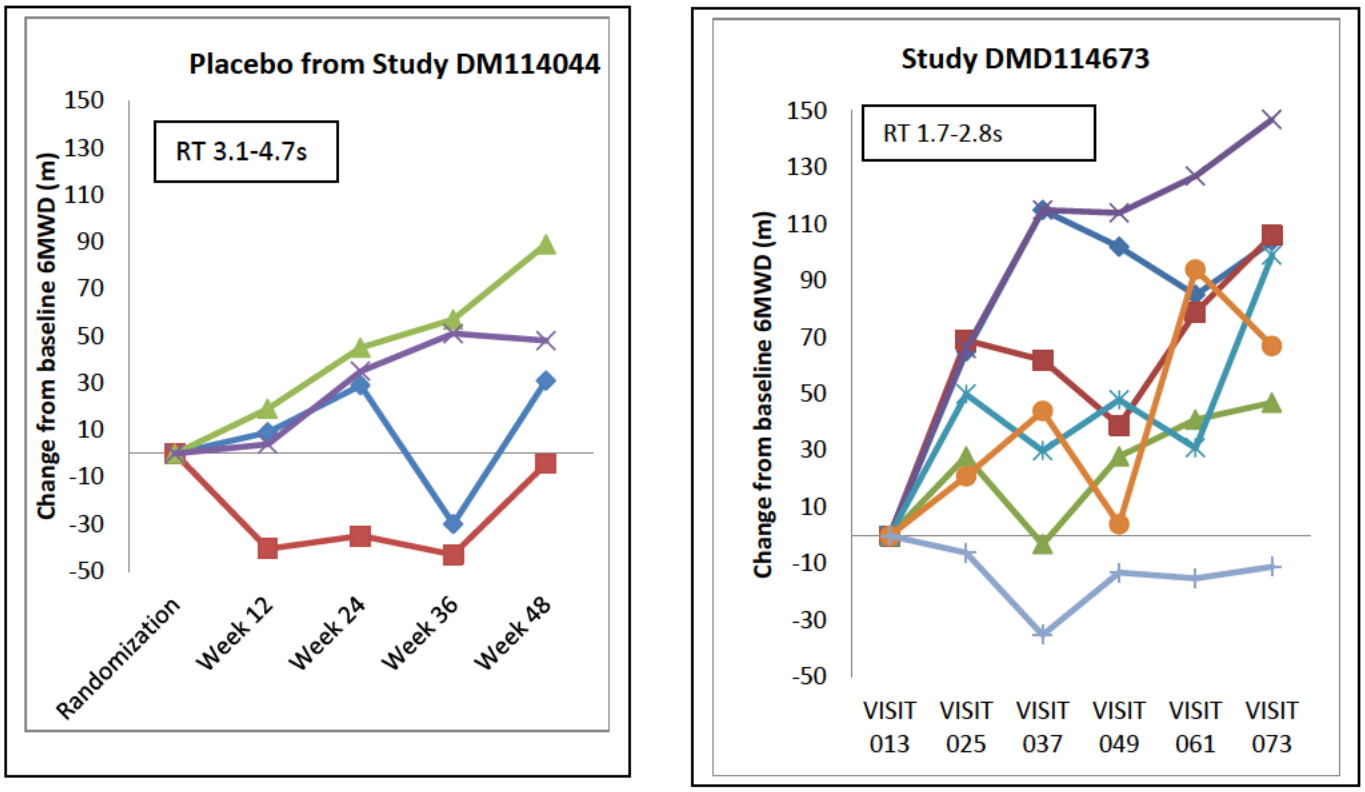


Subject	Baseline Rise Time	Baseline 6MWD
101	2.58	374
102	2.35	406
104	1.75	647
105	2.35	340
202	2.78	429
206	2.44	350
207	2.86	500

I looked at placebo subjects from Study DMD114044 that would be between the ages 8 and 14 years (for the 3+ years of study duration) and would have a rise time of < 5 seconds to match the baseline characteristics of the stable population in this study to explore the disease trajectory in such subjects. There were no matching subjects >10 years with similar characteristics. The "Stable" subjects in the open label study were atypical, that had extraordinarily low rise time from floor time, at an age when many patients with this genotype lose ambulation. As can be seen the Figure 26, placebo subjects in the similar baseline (age, 6MWD and Rise time) characteristics also show a gain in the 6MWD *over a year* of similar magnitude (up to 90 m). Subjects with low Rise from Floor Time appear to have a milder prognosis and can remain more functional for couple years before they begin to decline. For comparisons, I plotted the disease trajectory for the patients in this study up to 1 year.

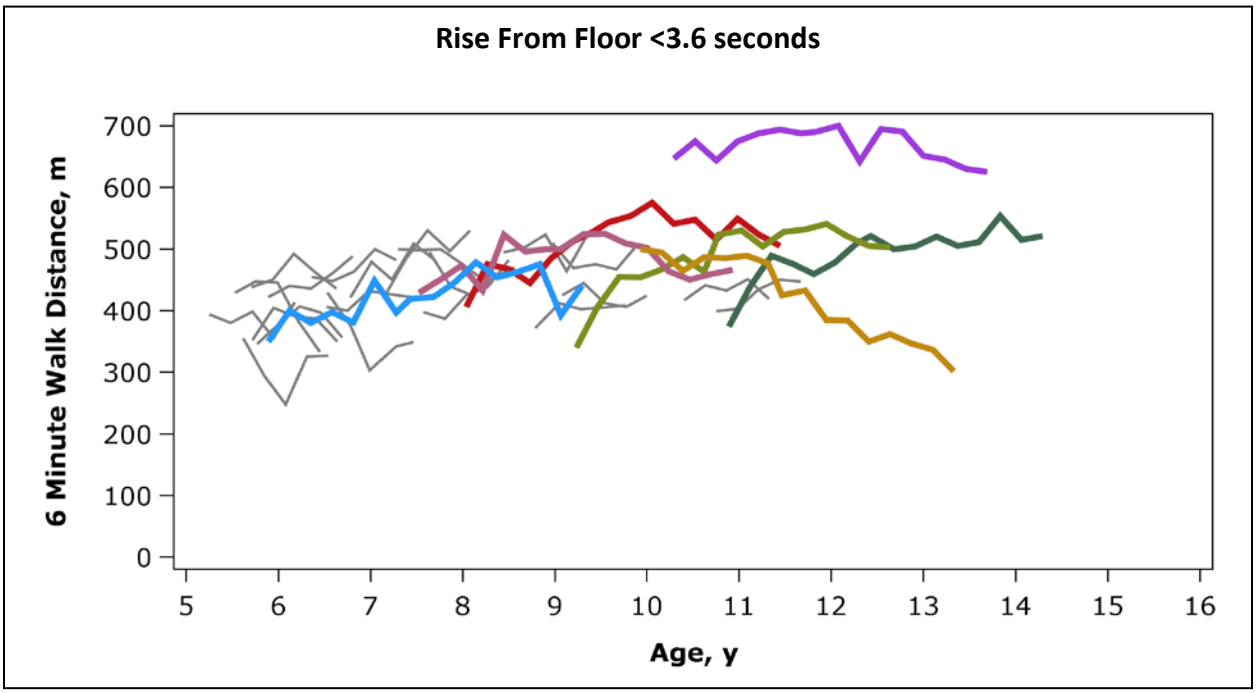
The disease trajectory in this one year duration appear similar, even though the placebo subjects from Study DMD114044 have baseline Rise from Floor *higher* (worse prognosis) than those in Study DMD114673. No other study in the application has a mean rise from floor time of 2.4s (Stable group). The mean rises from floor time in other studies range from 4.8-12.3s.

Figure 26 Comparisons of subjects with similar Time to Rise From Floor

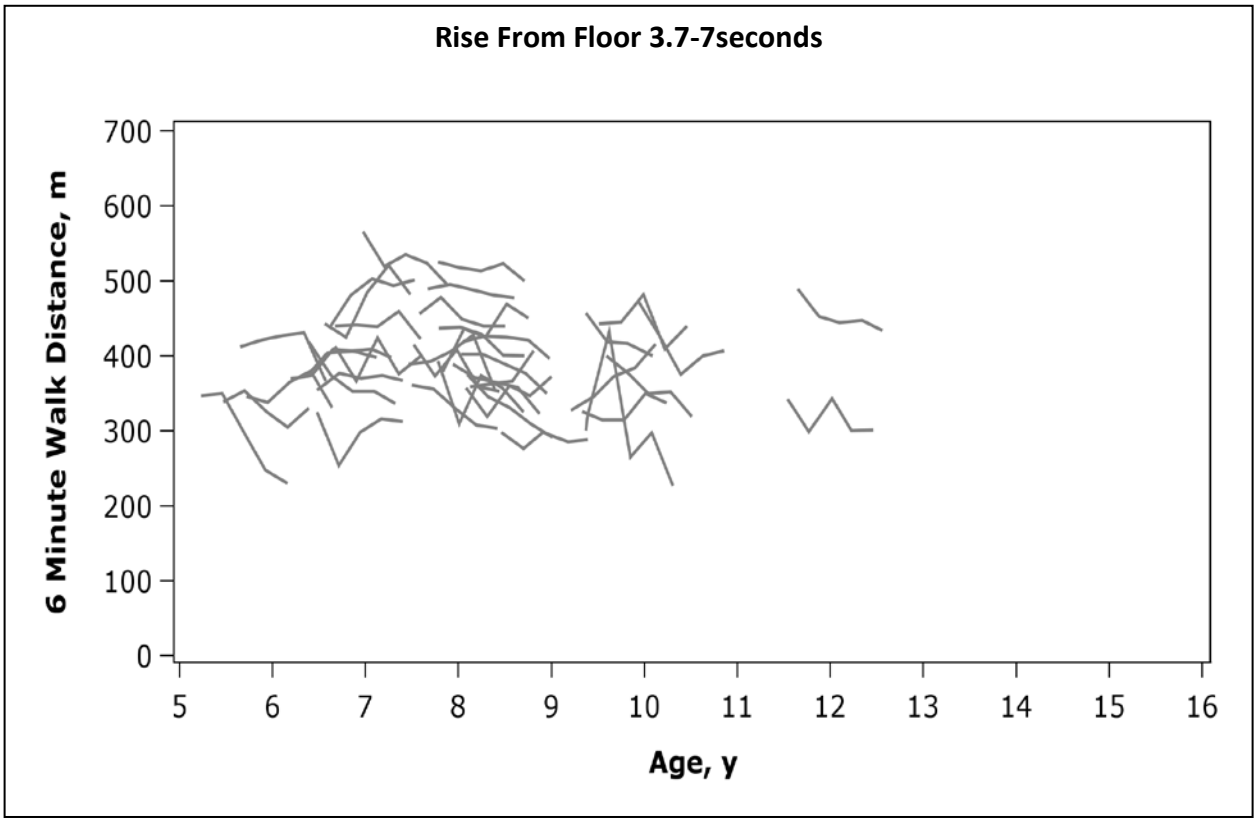


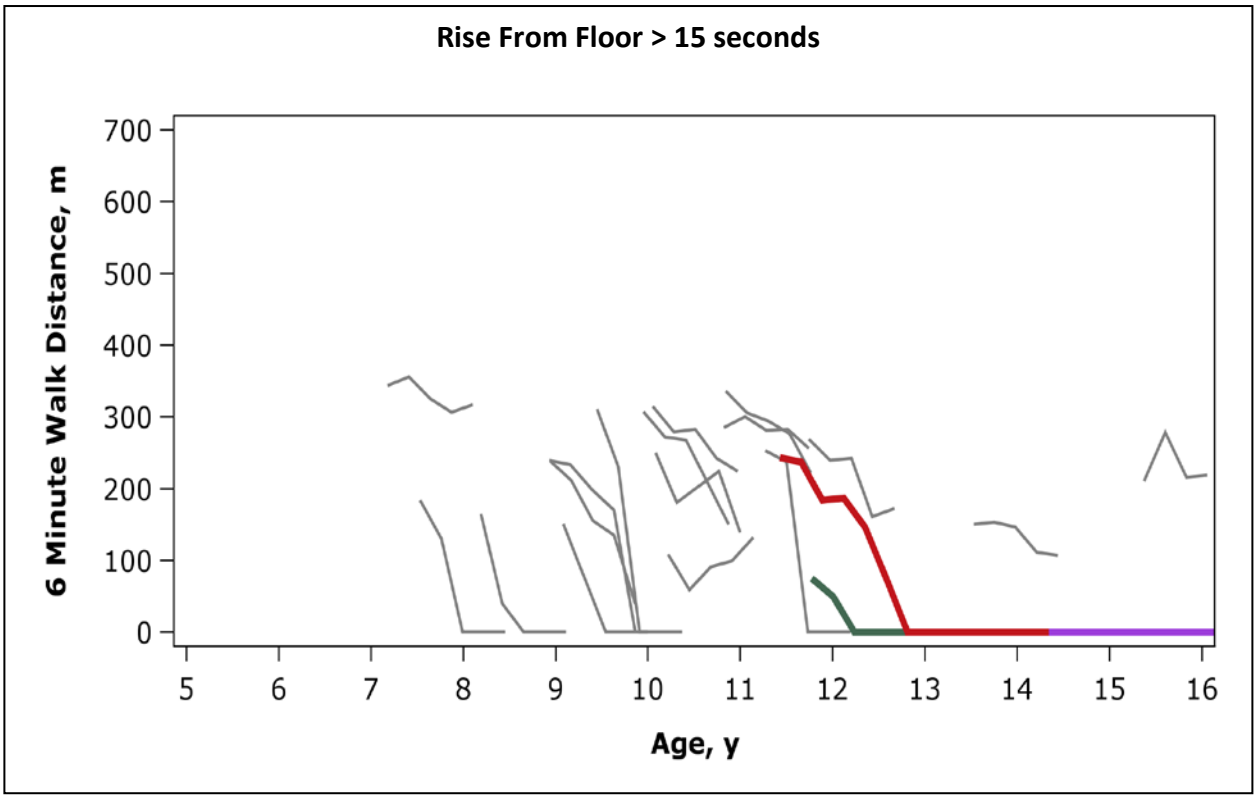
The 6MWD across all the placebo subjects from drisapersen studies, with Rise from Floor that match those from this Study DMD114673 was also looked at to evaluate the disease progression in these subjects. Rise from Floor from Study DMD114673 were lower than those found in the placebo subjects. The four different groups of baseline Rise from Floor were generated and the 6MWD was plotted as a function of age. The four groups were subjects with baseline Rise From Floor <3.6 seconds (to match the stable patients), 3.7-7 seconds, 7.1-15 seconds and >15 seconds. The 6MWD for each patient from this open label study was overlaid on the placebo subjects, to visualize the disease course of the subjects as shown in Figure 27. The figure shows that the disease progression of the subjects in Study DMD114673 is not different from placebo subjects from the drisapersen studies. The subjects that have higher function at baseline tend to show slower progression for few years.

Figure 27: 6MWD matching analysis with placebo subjects from drisapersen studies matched for baseline Rise From Floor Time



Note: Placebo data are shown in grey lines and all subjects from Study DMD114673 are shown in colored lines



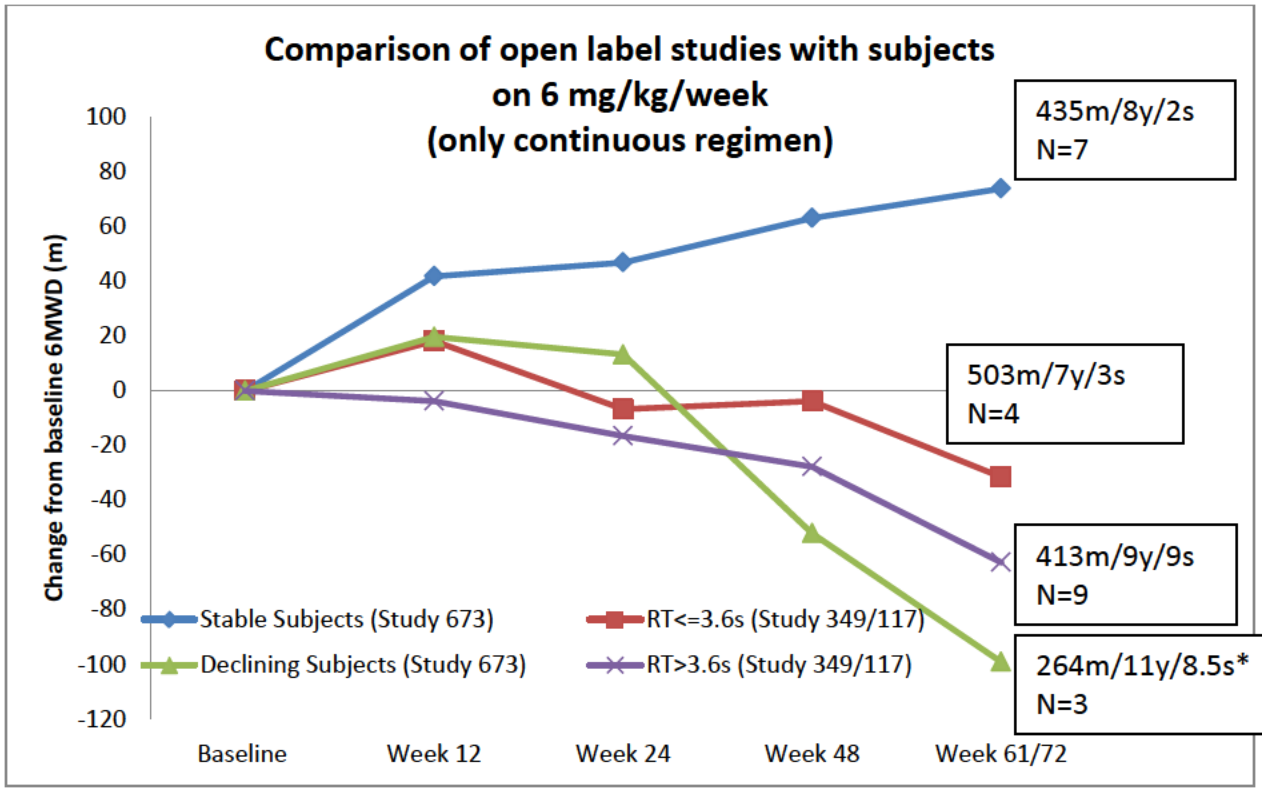


Source: Dr. Bhattaram

In addition, I also explored the differences in disease progression across the two open label studies (Study DMD114349 and Study DMD114673). I graphically compared the means profiles of "Stable" and "Declining" subjects from Study DMD114673 to the subjects from the Phase 2 study DMD114117 that were evaluated for 2+ years in the open label extension study DMD11349. Baseline 6MWD, age and Rise from Floor are provided in boxes for each group of patients. Three observations were made in this comparison based on the mean data for each group:

1. **Two small groups of patients in an open label setting can behave quiet differently such as the interpretation of small open label studies may be problematic (Figure 28, blue and red profiles.**
2. **The disease progression appears to be dependent on the baseline Rise from Floor, 6MWD and age. Subjects with milder disease at baseline tend to have a slower progression, as shown by grouping subjects with Rise from Floor <3.6 and >3.6 seconds. This makes it difficult to conclude that the slow progression is due to drug effect and not due to the natural course of the disease in such patients. With the lack of adequate long term natural history data in such patients with mild disease at baseline, any conclusions of drug effect appears problematic (Figure 28 and Figure 29).**
3. **The magnitude of decline also depends on the composition of the patients in a group. When subjects from the continuous and intermittent regimens were combined the magnitude of decline was greater (Figure 29 and Figure 30).**

Figure 28 Comparisons of open label studies with subjects on 6mg/kg/week



*Note: one subject was unable to Rise from Floor, two that lost ambulation not included, week 61 plotted for declining subjects

Figure 29 Comparisons of open label studies (Study DMD114117 regimens combined)

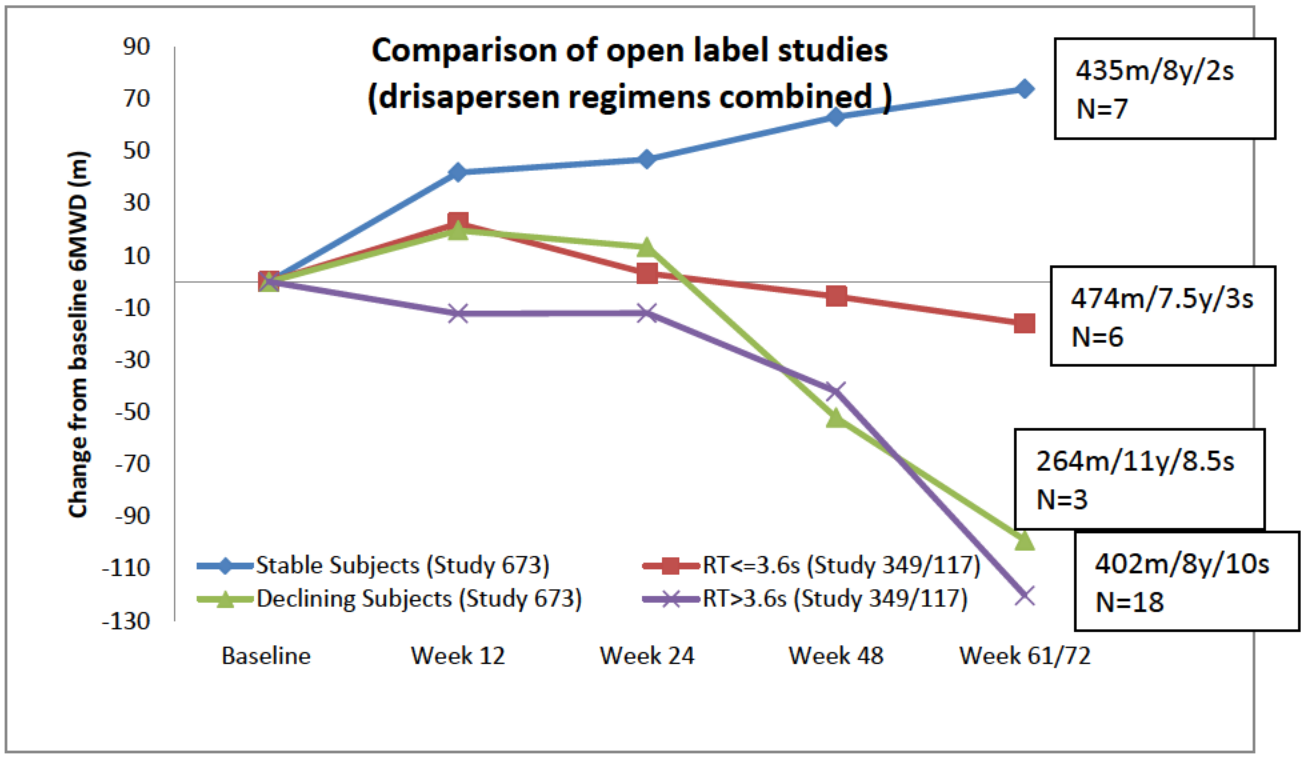
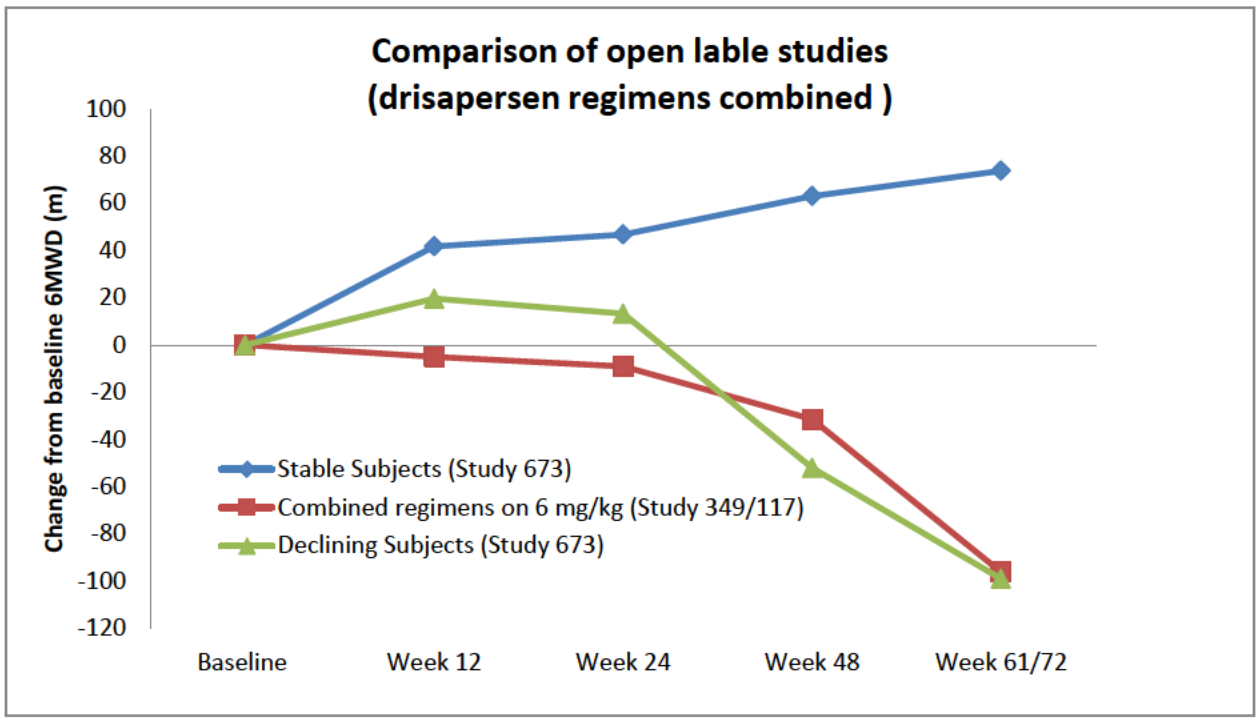


Figure 30 Comparisons of open label studies (Study DMD114117 regimens combined, not separated by Rise from Floor)



Therefore, age, 6MWD and rise from floor time all are important factors to determining the disease trajectory of a given patient, in additional to many other known and unknown factors, genetic modifiers etc. The subjects in this study appear to have a better disease prognosis. In the absence of a control group, this study therefore, does not show any interpretable evidence of a benefit from treatment with drisapersen.

6.6. **PRO051-02**

6.6.1. **Study Design**

Overview and Objective

This was a phase I/II, open label, escalating dose pilot study to assess the effect, safety, tolerability and pharmacokinetics of multiple subcutaneous doses of PRO051 in patients with Duchenne muscular dystrophy.
Study Period: 25 March 2008 to 25 May 2009
Study Centers: UZ Leuven (campus Gasthuisberg), Leuven, Belgium
The Queen Silvia Children's Hospital, Goteborg, Sweden

Trial Design

Doses: Dose escalation study with subcutaneous injection of 0.5, 2, 4 and 6 mg/kg once per week (N=3 in each group)
Medication was injected in the abdominal subcutis by a maximum of two subcutaneous injections.
Population: 12 DMD boys with mutation correctable by skipping exon 51

- Ages 5-16 years that had a life expectancy of at least 6 months and were not on ventilator support.
- Glucocorticoid use was to be stable for at 2 two months prior to enrolment, and was to be kept constant during the study.

At screening, an MRI was performed to assess the quality of the muscle in which the biopsy was planned.
Duration/Assessments: Treatment: 5 weeks (Days 1, 8, 15, 22 and 29), Follow up: 13 weeks (Days 36, 43, 57, 78, 99 and 120)
In the 0.5 mg/kg dose group, a muscle biopsy was taken at Visit 1 (Screening) and at Visit 8 (Day 43). In the other dose groups, a muscle biopsy was taken at Visit 8 (Day 43) and at Visit 10 (Day 78).

Study Endpoints

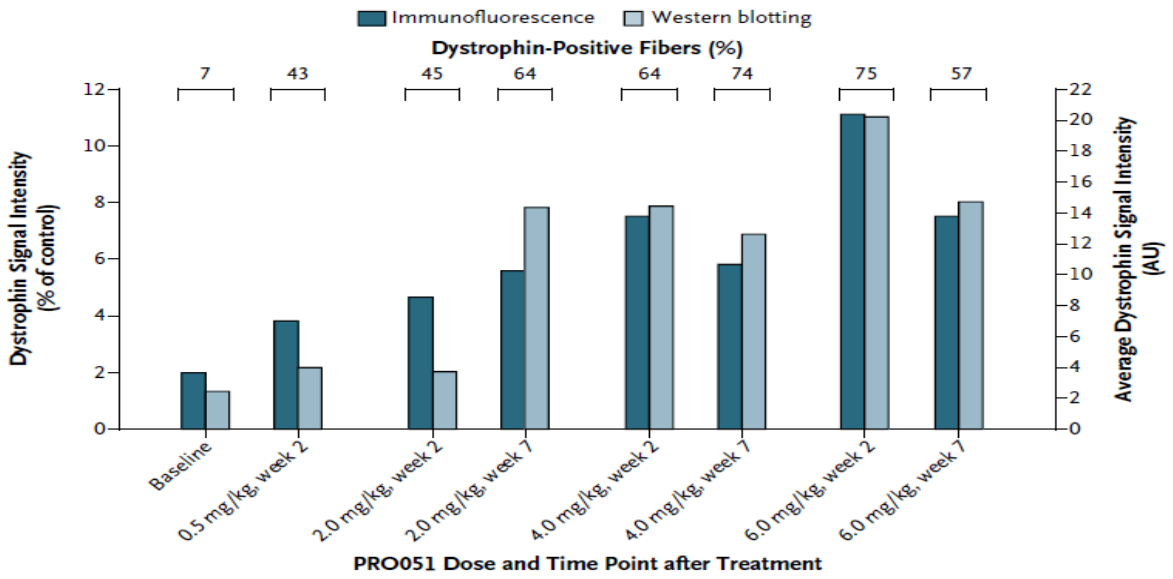
- Production of exon skip 51 mRNA and dystrophin expression by IFA and WB
- Presence of dystrophin expression (immunofluorescence analysis of cross-sections derived from muscle biopsy and Western blot analysis of total protein extracts from muscle biopsy)
- Muscle function (10m walk/run test, timed rising from floor, stair climb and 6MWT)
- Muscle strength

6.6.2. **Study Results**

In the 0.5 mg/kg dose group none of the subjects showed exon 51 skipping by RT-PCR. The effect in the 6 mg/kg dose group was not as prominent. Only the 4 mg/kg group showed exon 51 skip in all subjects. Average number of dystrophin positive fibers and average dystrophin signal intensity increased with increasing dose at 2 and 7 weeks after treatment.

The applicant refers to the published article by Dr. Goemans, which states that new dystrophin expression was observed between 60-100% of muscle fibers in 10 of the 12 patients, which increased in a dose dependent manner to up to 15.6% of the expression of healthy muscle.

<u>Reviewer's Comment:</u> It is unclear how dystrophin was detected 2 and 7 weeks after 5 doses in this study, when in no other study dystrophin was detected after 12 weeks of continuous dose of 6 mg/kg/week. The applicant has not provided individual raw data for this study to support the numbers for the dystrophin positive fibers, but refers only to the published article. There were no pre-treatment assessments at all doses, but only for the low dose (0.5 mg/kg) which is represented as the baseline in the above figure.

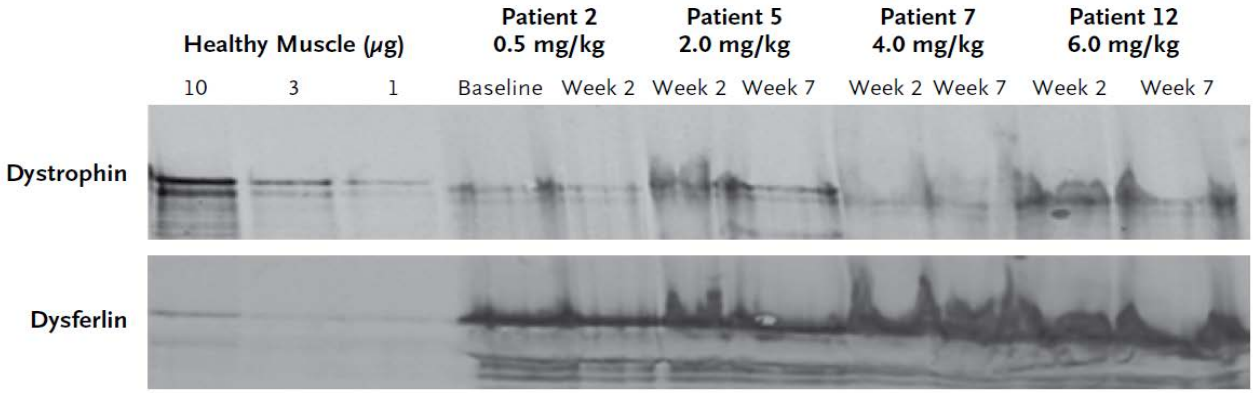


Source: Goemans NEJM 2010

<u>OBP Reviewer Dr. Rao comment on methodology:</u>

The publication states that "a signal intensity of 15.6% of the control intensity in Patient 8." However, no raw data for patient 8 is provided in the publication. Overall, they comment that "The amount of dystrophin ranged from 17 to 35% of control levels." However, a baseline sample was not tested in 9 out of the 12 patients. It is also noted that the western blot image in the NEJM publication is of <u>*extremely poor quality*</u> because the dystrophin bands are not clearly discernable, there is substantial smearing of the bands into other lanes, air bubbles or other artifacts, and the loading control (dysferlin) appears to be <u>*unusable*</u> for densitometric

quantitation and normalization of dystrophin. While the healthy control dilutions appear to suggest that dystrophin levels comparable to or higher than these dilutions were observed in post-treated samples, the dilution factor between the healthy and DMD samples was between 300-500 fold, suggesting that post-treatment levels were extremely low compared to normal. Furthermore, linearity cannot be assumed at this high dilution.



6.7. **Other Studies: DMD PRO051-01**

Study PRO051-01 was an exploratory Phase 1 single dose, open label study in 4 ambulant and non-ambulant DMD subjects to evaluate the local dystrophin production after localized intramuscular injection. The primary data was not submitted to the NDA, and the following description is based solely on what was reported by the authors of the published report. Subjects were administered 0.8 mg drisapersen intramuscularly. The amount of dystrophin in total protein extracts ranged from 3 to 12% of that found in the control specimen and from 17 to 35% of that of the control specimen in the quantitative ratio of dystrophin to laminin α2.

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy across Trials

7.1.1. **Primary Endpoints**

The Applicant conducted three randomized, double blind placebo controlled trials:

1. Study DMD114117 (n=53): evaluated two different regimens (continuous and intermittent) of the same dose (6mg/kg); Primary endpoint was change from baseline 6MWD at Week 25.
2. Study DMD11476 (n=51): evaluated two doses(3 mg/kg/week and 6 mg/kg/week); primary endpoint was at Week 24
3. DMD114044 (n=186):evaluated a single dose (6mg/kg/week), primary endpoint was at Week 48

In addition, the NDA included two open label extension studies Study DMD114349 (the 120 week extension of the placebo controlled studies: DMD114117 and DMD114044), and Study DMD114763

(the 3.5 years extension of a 5 week proof of concept study PRO-051-02). In the extension studies subjects were given 6 mg/kg/week, but subjects had the option of moving to the intermittent regimen or to discontinue for safety related reasons.

6MWD is considered an effort dependent endpoint. The unblinding due to injection site reactions observed in the drisapersen treated subjects could potentially bias the results obtained from an effort dependent endpoint.

The strength and weaknesses of the analysis of the primary endpoint for the three placebo controlled studies are summarized below:

- Study DMD114117: The primary endpoint, change from baseline 6MWD at Week 25 was statistically significantly different from placebo for the continuous 6mg/kg/week dose with a treatment difference of 35 m (p=0.01) over placebo. Some of the weaknesses of the study include:
    - *Lack of treatment benefit with intermittent regimen*: a non- significant p-value of 0.80 at 24 weeks for the intermittent regimen which had comparable total doses and identical plasma concentration time profile and should seemingly produce similar response to treatment.
    - *Decline at Week 49*: The change from baseline in 6MWD of 31 m observed at Week 25 does not appear sustained at Week 49 with a decline to 11 m. Such differences could also be observed due to variability that may make the results look worse than they are (such as at Week 49) and make the results look better than they are (such as at Week 25). The improvement seen at Week 25 followed by a decline at Week 49 in the continuous drisapersen treatment group is concerning.

The subjects in the continuous treatment arm comprised of patients that were more functional at baseline compared to the intermittent and placebo arms as discussed in section 6.1.2. Differences in the baseline functional abilities of subjects in the treatment groups could bias the interpretation of the results. A small study increases the risk that efficacy may reflect baseline imbalances. Subjects with milder disease progression and younger age may remain stable or improve for the duration of 48 weeks or more. (McDonald 2013).

Since the continuous and intermittent regimen, both consisted of the same 6 mg/kg dose, a post-hoc analyses combining the two treatment regimen, showed a treatment difference over placebo of 31 m (nominal p=0.05) at Week 49, but a treatment difference of 20 m (p=0.12) at Week 25. This post-hoc analysis may suggest a lean towards treatment benefit at week 48 with drisapersen for a phenotypic heterogeneous DMD population, although unblinding due to injection site reaction remains a concern.

- Study DMD114876: The primary endpoint, change from baseline 6MWD at Week 24 for the 6mg/kg/week dose showed a treatment difference over placebo of 27 m (p=0.07) that was not statistically significantly different from placebo. Ordinarily this would be considered a negative study, but for a disease with no approved treatment, this could be considered as supportive evidence of benefit. Additional weaknesses of the study include:
    - In applicant's sensitivity analysis, removing a single placebo subject whose treatment was unblinded due to a hospital visit for flu-like symptoms, a treatment difference of 19 m (p= 0.21) was observed, further weakening the confidence in the evidence towards efficacy.

- A lower 3 mg/kg/week dose was worse than placebo. This suggests that the disease trajectory of patients with DMD is dependent on their baseline disease characteristics as discussed in section 6.2.2.
- This was a 24 week study. A 48 week Study DMD114117, showed at decline from baseline at Week 48. In Study DMD114876, the 6 mg/kg/week group showed stability in 6MWD up to Week 48, even when no treatment was given beyond 24 weeks. This could be due to variability or that subjects follow their own disease trajectories based on the baseline characteristics. Natural history studies by experts in the area suggest that earlier functional abilities can predict later functional abilities.

- Study DMD114044 (2:1 randomization): The change from baseline at week 48 for the 6 mg/kg/week dose was 10 m (p=0.42) that was not statistically significantly different from placebo. Applicant's discussion on the lack of response in study DMD11404 is given in section 6.3.3. Overall, this study was a well-designed and executed study with good statistical power to detect a small treatment effect.

The change from baseline and magnitude of treatment difference in these placebo controlled studies is summarized in Table 48 on page 116:

The open label studies with drisapersen are not supportive of treatment benefit.

- A 120 week open-label extension Study DMD114349 appears uninterpretable as many subjects dropped out either due AE or the study being terminated early (4/18 on placebo and 5/35 on treatment from Study DMD114117). The decline in 6MWD in each treatment arm based on the parent study (DMD114117 and DMD114044) appears to be consistent with the phenotypic heterogeneity of each arm (see discussion in section 6.4.4), with the more functional subjects at baseline showing a slower progression and less functional patients at baseline showing a larger decline in a year. The applicant asserts a treatment difference of 50m at Week 96 for subjects on the continuous regimen compared to the placebo group that switched to treatment. The Applicant discusses the extension of DMD114117 only based on the subjects that were on continuous 6mg/kg/week regimen, that appeared more functional at baseline compared to the subjects on the intermittent regimen. The subjects on intermittent regimen when switched to the continuous regimen after 48 weeks show a treatment difference of 8m at Week 96 compared to the placebo group that switched to treatment. The subjects on intermittent regimen showed a mean decline in 6MWD of 63m at Week 96. It is known that the disease course is highly variable between affected individuals, a striking example being the age for the loss of ambulation, which can range from 6 to 15 years (Flanigan 2013, Hembertclaude 2102) and higher baseline function is associated with slower long-term decline in DMD (McDonald).
- A 3.5 years long open label study DMD114673 in 12 subjects showed that only 5 subjects did not decline during this study and 3 lost ambulation. The subjects that declined did not appear to be different from the typical natural history control. The subjects that did not decline in Study DMD114673 were atypical. They were highly functional at baseline with Time to Rise from Floor of <3seconds. ***There were no other patients in the entire drisapersen development program with such low Time to Rise from Floor***. Consequently, it is entirely unconvincing that the stability observed in these 5 subjects is a treatment effect.

Table 48 Primary endpoint analysis from the three placebo controlled studies (primary endpoint in orange colored boxes)

	Phase II studies						Phase III study	
	DMD114117			DMD114876			DMD114044	
	Placebo (combined) (N=18)	Drisapersen 6 mg/kg/wk (N=18)	Drisapersen 6 mg/kg intermittent (N=17)	Placebo (combined) (N=16)	Drisapersen 3 mg/kg/wk (N=17)	Drisapersen 6 mg/kg/wk (N=18)	Placebo (N=61)	Drisapersen 6 mg/kg/wk (N=125)
Baseline, n Mean								
Week 24 n **Mean change** Treatment difference p-value	16 **–4** 	16 **31** 35 0.01	15 **–0.1** 4 0.80	16 **–11** – –	17 **–20** **–9** 0.55	18 **16** 27 0.07	59 –29 – –	122 –24 5 0.63
Week 48 n **Mean change** Treatment difference p-value	17 –25 – -	18 11 36 0.05	15 2 27. 0.15	15 -13.17 – –	17 -38 -25 0.24	18 15 28 0.18	59 **–52** – –	117 **–42** 10 0.42

No treatment

Source: Adapted from Applicant's analysis with FDA re-evaluation

The conflicting, results from Study DMD114044 diminish the strength of the smaller studies. One of the explanations by Applicant for this negative study has been the demographic and baseline population make-up of the Phase II and Phase III studies. As shown in the Table below, the smaller studies had a slight younger and more functional population in the continuous 6 mg/kg/week arm compared to the larger negative study.

Study	Prognostic Factor	Placebo	Drisapersen 6 mg/kg/week
DMD114117 (N=53)	Median Age (years) Baseline 6MWD (m)	7 years 403 m	6.5 years 428 m
DMD114876 (N-51)	Median Age (years) Baseline 6MWD (m)	8 years 416 m	6.5 years 396 m
DMD114044 (N-186)	Median Age (years) Baseline 6MWD (m)	8 years 348 m	8 years 337 m

Based on mean/median age and mean 6MWD at baseline, it appears true that the DMD subjects in Study DMD 114044 are likely to be more progressed in their disease. No restriction on the rise from floor was the only difference in the enrollment criteria between these studies. I looked at a subset of subjects from this study that had the similar age distribution (5-13 years), same range of 6MWD at baseline (330-561m) and subjects with rise time of ≤7 seconds as in the smaller studies to match the patient population characteristics in the Phase 2 and 3 studies. The MMRM analyses were conducted by Dr Sharon Yang (Statistician). The subjects in this subgroup of Study DMD114044 are balanced with regards to their age, baseline 6MWD and rise from floor time as shown below.

Study DMD114044 Subset with Subjects that meet the following criteria: Ages 5-13 years 6MWD 300-561m RT ≤7 sec	Prognostic Factor at baseline	Placebo N=27	Drisapersen 6 mg/kg/week N=59
	Median Age (years) Mean Age (years) Mean 6MWD (m) Median 6MWD (m) Mean Rise from Floor (s) Median Rise from Floor (s)	7 years 6.8 years 401 m 399 m 4.44 s 4.1 s	7 years 7.2 years 402 m 402 m 4.84 s 4.9 s

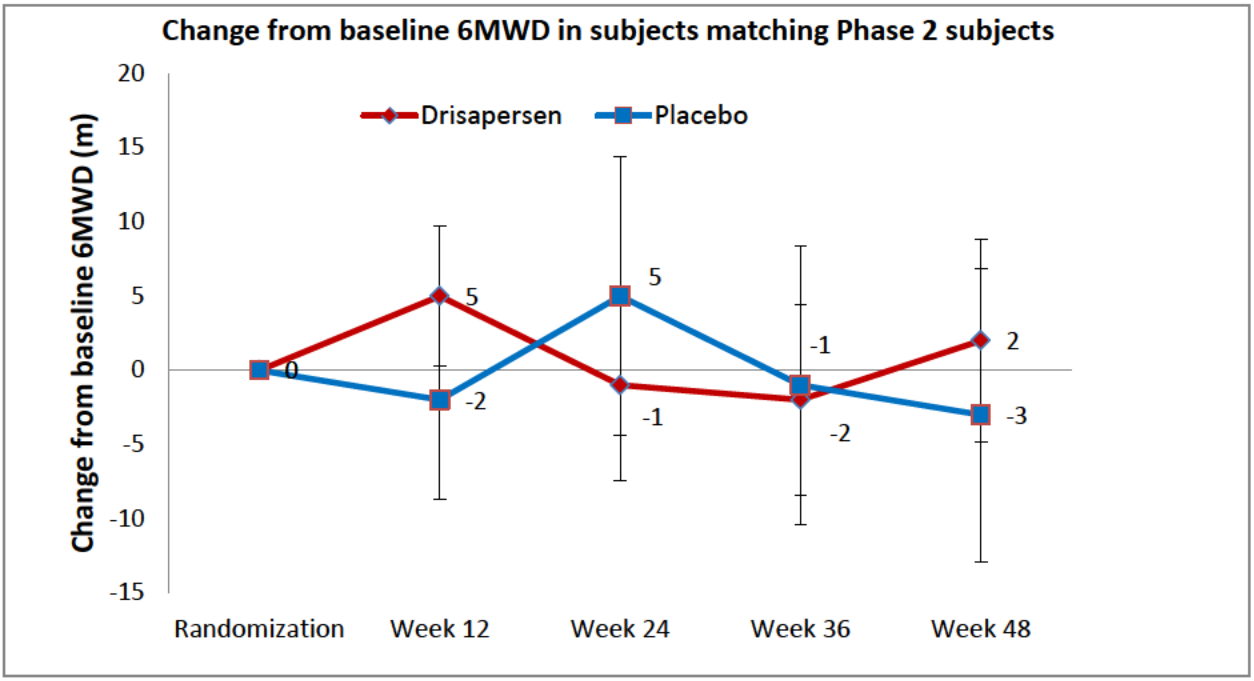
This subset of patients from Study DMD114044, showed a mean treatment difference of 5m, suggesting that the severity of the disease is not the reason for the negative results in study DMD114044 (Table 49). The results from this post-hoc analysis are contradictory to the results obtained from Study DMD114117. This also suggests that chance baseline imbalances, not drug effect, led to the positive findings in study 117.

Table 49 FDA analysis of subjects from Study DMD114044 that match the subjects from Studies DMD114117 and DMD114876

	Placebo (n=27)	Drisapersen 6 mg/kg/week (n=59)
Week 48		
Adjusted mean change	-3	2
Adjusted mean difference vs. placebo		5
p-value		0.71

Figure 31 shows the adjusted mean change from baseline in subset of subjects from Study DMD114044 that match the baseline characteristics of subjects from the Phase 2 studies.

Figure 31: FDA analysis of subjects from Study DMD114044 that match the subjects from Studies DMD114117 and DMD114876



I also conducted Kaplan-Meier analysis showing time to persistent 10% worsening in 6MWD in subjects with rise from floor ≤7 seconds. No meaningful differences between treatment groups were observed. Hence, the applicant's argument of a more functionally impaired population of the Phase III study as the reason for a negative study is not convincing.

The applicant presents the argument in the ISE that certain subgroups based on age (≤ and >7 years) and 6MWD (±330) may respond differently. The applicant's post-hoc analyses showing the treatment

differences in the four subgroups based on age and 6MWD are presented in Table 50.

Table 50 Mean/Median Change of baseline 6MWD by age group and 6MWD (applicant's post-hoc analysis of Study DMD114044)

	Age ≤ 7 years				Age > 7 years			
	6MWD ≤ 330 meters		6MWD > 330 meters		6MWD ≤ 330 meters		6MWD > 330 meters	
	6 mg/kg	Placebo	6 mg/kg	Placebo	6 mg/kg	Placebo	6 mg/kg	Placebo
N	17	4	33	25	33	17	34	13
Mean	11	-62	-12	-18	-124	-108	-25	-52
SD	49	99	63	51	94	108	61	70
Median	**23**	**-55**	**-7**	**-26**	**-109**	**-109**	**-22**	**-55**
Min	-109	-184	-215	-96	-303	-311	-194	-185
Max	68	42	112	106	48	89	102	48
Difference in Medians	**+77 p=0.01**		**+20 p=0.66**		**-0.2 p=0.48**		**+33 p=0.24**	
Difference in Means	**+75 m**		**+6 m**		**-16 m**		**+27m**	

Source: NDA module 2.5 Clinical Overview page 52

A treatment difference of 75 m (p=0.012) was observed for the sub-group age ≤7 years and 6MWD of ≤330 m. The treatment effect observed in the smaller studies was not likely driven by this subset of the patients, as there was only 1 subject each in the 6 mg/kg/week treatment group in both the Phase II studies with a baseline 6MWD of ≤330 m. Secondly, the median treatment difference of 75 m in Age ≤7 years + 6MWD of ≤330 m subgroup is driven by one placebo subject (#1256) with a baseline 6MWD of 184 m who could not perform the 6MWD due to gait loss after Week 12, hence at all subsequent visits the 6MWD was imputed to zero. Removing this subject, the treatment difference in the group of patients Age ≤ 7 years + 6MWD≤ 330 m is 10 m. The other subgroups did not have a nominally positive p-value, including the subgroups that would likely have a milder progression (Age ≤7 years + 6MWD of >330 m, Age >7 years +6MWD of >330 m). Lastly a 6MWD of 330 m is a subjective cutoff. In the published literature some experts have presented natural history data in DMD with a cutoff of 350 m.

In an amendment to the ISE submitted on August 31st 2015, the applicant conducted additional analysis using an enhanced MMRM model including age and 6MWD subgroup and treatment by age and subgroup interaction as terms in the model. This analysis showed a treatment difference of 20 m (p=0.12) (Table 51). Baseline 6MWD was accounted for redundantly as terms in this model. Please refer to the statistical review for limitations on the statistical model.

Table 51: Applicant's post-hoc analyses of Study DMD114044

Model	Population	Placebo (adjusted mean)	6mg/kg (adjusted mean)	Treatment effect vs. Placebo	P-value of Treatment Difference
MMRM	Overall*	-60 m	-40m	+20 m	0.12
MMRM	Overall ** minus older/more severe group based on 6MWD cut off of **330m**	-44 m	-11m	+33 m	0.01

Source: Sponsor ISE amendment, Aug 31st 2015

The applicant asserts a treatment benefit of 33 m (nominal p-value 0.01) after removing subjects that are of Age > 7 years + 6MWD≤ 330 m as it was the only subgroup that did not show a treatment benefit. By removing only one placebo subject that could not perform the test the p-value increases to 0.06. Using a 6MWD cutoff of 350m p-value increases to 0.06 with a treatment difference of 23 m and removing the single placebo subject (#1256) the p-value increases to 0.12 (Table 52), further suggesting that the results are dependent on the way the cutoff points are drawn are appear unstable.

Table 52 FDA Analysis with a 6MWD cutoff of 350m

Model	Population	Placebo (adjusted mean)	6mg/kg (adjusted mean)	Treatment effect vs. Placebo	Nominal P-value of Treatment Difference
MMRM	Overall ** minus older/more severe group based on 6MWD cut off of **350m**	n=39 -33.8 m	n=81 -10.4m	+23.4 m	0.062
MMRM	Above population minus subject #1256	n=38 -26.9	n=81 -10.7	+16.3	0.196

Source: Dr. Sharon Yan

Hence, the sponsor's argument of removing a subgroup to show treatment benefit is subjective, as the effect size appears unstable and the p-value changes.

Overall, the evidence of efficacy from these studies based on the primary endpoint change from baseline 6MWD appears uncertain. The increase from baseline in 6MWD observed at Week 25 does not appear sustained at Week 49. The results from the other two studies further mitigate the positive findings from Study DMD114117, although a numerical advantage at Week 48 can be argued. It is difficult to separate a treatment effect from unblinding biases. Some of the many factors that could introduce bias studies could be clear unblinding due to injection site and physical training. Physical training might delay the functional deterioration caused by disuse in boys with DMD (Jansen 2013). From the open label studies, there is no reliable estimate of what happens to the subjects over several years due to dropouts. Overall, a precise estimate of treatment benefit cannot be established. Even if we assume a short term treatment benefit of 10-20m based on the overall results, there is no clear way to estimate whether this would delay the time to loss of ambulation. In addition, switching subjects from an intermittent regimen from Study DMD114117 to continuous regimen in the second year, subjects appear to be headed to losing ambulation at an age not older than expected from

natural history. The prognosis of subjects is dependent on their baseline function.

Given the heterogeneity in disease progression, stratification of patients was important to ensure the groups were balanced not only for age, but for baseline 6MWD and corticosteroid use (McDonald 2103). It also appears that other factors such as Time to Rise from Floor, Ability to jump or hop clearing both feet up, ability to rise with gower's maneuver may also be important factors in predicting disease progression. The knowledge of these factors became apparent after these studies were initiated. In general, the pathophysiological mechanisms that underlie phenotypic variability are not fully understood. Recent publications also suggest genetic modifiers such as LTBP4 and osteopontin that could predict the disease trajectory in individual subjects. Such information is not available from the drisapersen program.

7.1.2. **Secondary and Other Endpoints**

None of the secondary endpoints showed statistically significant treatment difference at either Week 24 or 28 in the three placebo controlled studies. The secondary endpoints were not analyzed in a hierarchical manner in the small studies (DMD114117 and DMD114876) and no key secondary endpoint was identified. In the large Study DMD114044, NSAA, 4-stair climb-ascent and 10 m walk/run were assigned as key secondary endpoints. The applicant does not propose labeling claims based on any secondary endpoints. All conclusions from all secondary endpoints are briefly summarized below:

Timed Function tests (rise from floor, 10 m walk/run, and 4-stair climb/ascent-descent):

- In Study DMD114117, the timed function tests were in the same direction as the primary endpoint for the continuous 6 mg/kg/week group compared with placebo was observed at Week 25 and 49. The trend of improvement worsened at Week 49, but remained numerically better than placebo. The clinical meaningfulness of these trends is unclear as the changes in the Timed Function Tests were less than 1 second, with the exception of rise from floor where a treatment difference of 3 seconds was observed. The intermittent regimen showed a favorable trend only for the 10 m walk/run.
- In study DMD114876, the timed function tests were variable with no consistent dose trends and the treatment difference was<1 second.
- In Study DMD114044, no consistent trends in favor of drisapersen were observed across all tests that are correlated with each other.

NSAA

- In Study DMD114117, NSAA showed favorable trends at Week 25 for both continuous and the intermittent regimen, that worsened at Week 49. The change from baseline in favor of drisapersen was greater for the intermittent regimen at Week 25, which does not follow the same direction as that of the 6MWD. The changes are small at week 49 (-0.2 and -0.4, respectively for the continuous and intermittent) in a total NSAA score of 34, with higher scores being better). Mazzone et al 2013 have shown that younger subjects can remain stable in NSAA assessments in the first year and there were a larger number of younger subjects in this study. Therefore, it is unclear if the stability is related to treatment effect or the natural progression of the disease as measured by NSAA.
- In study DMD114876 and DMD114044, no significant or consistent treatment difference in favor of drisapersen was observed.

Pulmonary Function Tests

- The changes in pulmonary function tests were small, not clinically meaningful in any study and not in favor of drisapersen. Changes in pulmonary function are not expected in early ambulant population.

Muscle Strength

- Unfavorable and variable trends in muscle tests were observed in all studies, with greater decline in muscle strength observed in the drisapersen group in Study DMD114044.

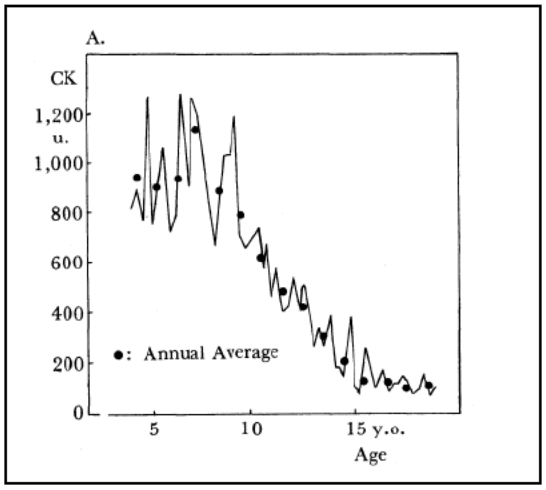
Serum Creatine Kinase:

Serum creatine kinase, a marker of muscle cell injury was the only secondary endpoint that was consistently reduced by 30-40% across the three studies based on percent change from baseline with nominal p-values of 0.08, 0.53 and <0.001 for the Study DMD114117, DMD 114876 and DMD114044 respectively, suggesting a possible improvement in muscle cell integrity. However, this finding is associated with several confounders: CK levels are remarkably variable, with large within patient and between patient variability and are known to fluctuate day to day. It is reduced with inactivity, steroid use, advancing age of the DMD boys due to reduction in muscle mass as the muscle fibers are replaced with fat and fibrous tissue, clinical progression and diurnal variation (increase during the day and decrease at night) and inflammation. I will evaluate each of these factors as possible confounder of a treatment effect.

- *Effect of variability on CK:* Statistically significant reductions in CK were observed despite the variability. CK increases during the day and decreases at night. All CK assessments in the studies were generally conducted between 8 am to 5 pm.
- *Effect of inactivity on CK:* Florence et. al. (1985) have shown that on complete bed rest days the mean decrease in CK level was 13,000 IU/L compared to the active days in DMD boys. The mean decrease in the drisapersen treated subjects in all the three studies was between 4000-5000 IU/L. There was no evidence of inactivity of the subjects from the Patient or Parent reported outcomes but the activity level of subjects are hard to discern from such studies and activity levels were not recorded systematically. The greater number of subjects with injection site reactions in the drisapersen treated patients could plausibly make the subjects less active, but CK reduced in subjects with or without injection site reactions to the same extent of 30-40%.
- *Effect of steroids on CK:* Steroid use reduces CK. Both drisapersen and placebo subjects were on steroids for a minimum of 6 months. It is not known if the dose, regimen and duration of steroid use would impact the reduction in CK. The impact of these on the reduction in CK across treatment groups are difficult to discern from the studies. There were some differences in steroids use across studies as shown below, but the impact of these difference is unknown:

	Study DMD114044		Study DMD114117		Study DMD114876	
	Placebo	Drisapersen	Placebo	Drisapersen	Placebo	Drisapersen
Median Time on steroids (months)	19	27	23	14	39	19
Steroid Regimen: Continuous (%) Intermittent (%)	 85% 15%	 86% 14%	 61% 39%	 67% 33%	 94% 6%	 100% 0%

- *Effect of age on CK:* Published studies suggest that CK peaks at ages 3-5 years and declines with age with levels reduced to 50% by age 7 years. Konagaya et. al. (Figure on the left) suggest that in the second half of the first decade, due to relatively higher rate of muscle degeneration, there is an abrupt drop of serum CK levels. Hence, CK decreases with age and disease progression. In study DMD114044, there were 17% subjects that were greater than 11 years in the drisapersen group compared to 11% in the placebo group. The Phase 2 studies had only couple subjects that were older than 11 years, about an age when there is an abrupt drop in CK levels. To explore if the statistically significant reduction in CK in Study DMD114044 was driven by the slightly higher number of subjects >11 years in the drisapersen group, I also calculated the mean percent change from baseline in CK in subjects >7 to ≤11 years in both drisapersen and placebo groups. Irrespective of the age groups CK was consistently reduced in the drisapersen treated patients compared to placebo patients as shown:



Mean percent change from baseline in CK	Study DMD114044		Study DMD114117 At Week 48		Study DMD114876 At Week 24	
	Placebo	Drisapersen	Placebo	Drisapersen	Placebo	Drisapersen
≤ 7 years	4.5%	-19%	36%	-11%	-2%	-31%
>7 years	-2%	-41%	36%	-41%	5.7%	-16%
>7 to ≤11 years	0.4%	-43%				

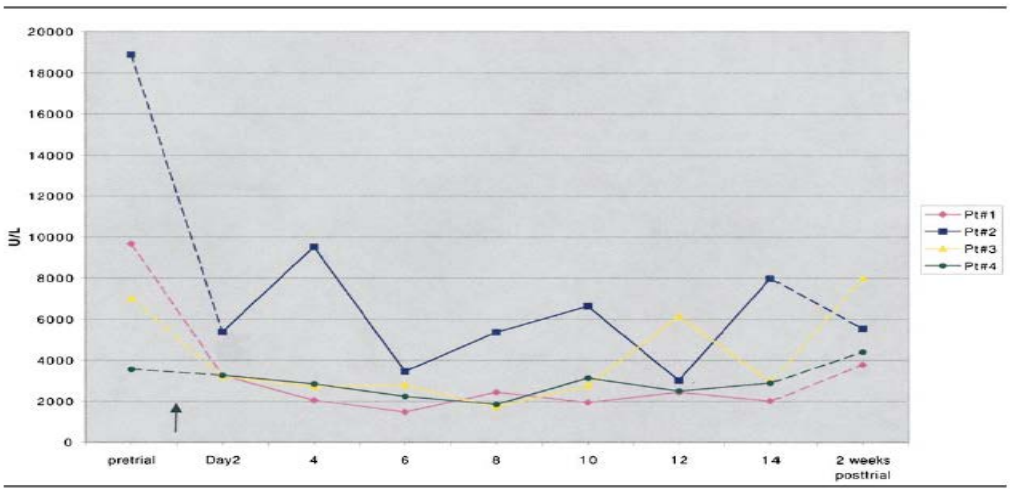
There was no consistent trend in mean percent reduction of CK in subjects <7 or >7 years and ranged between 30-40% reduction in these groups with wide variability. The percent reduction in the >7 years of age was 40% in Studies DMD114117 and DMD114044, and was 11-19% in subjects ≤7 years of age. Opposite trend was observed in Study DMD114876 subjects where subjects ≤7 years of age had greater reduction in CK (30%) compared to 16% in subjects >7 years of age. In addition, impact of reduction in muscle mass due to muscle wasting with increasing age is unknown from these studies, but muscle mass will decline with age and disease progression.

Nevertheless, CK reduction was greater in the drisapersen treated subjects in all three subjects with nominal p-values of <0.001, 0.08 and 0.53 from Studies DMD114044, DMD114117 and DMD114876, respectively.

- *Effect of inflammation on CK:* Reduced CK activity in inflammatory diseases such as rheumatoid arthritis is linked to an inflammatory response, where an inverse correlation has been reported between CK activity and inflammatory markers (Lee 2000). I explored if the decrease in CK in the drisapersen treated subjects was due to an increase in inflammation and not an improvement in muscle cell integrity. Only ≤10% of subjects on drisapersen showed elevation in

one of the inflammatory markers. The markers of inflammation, C-reactive protein and Complement C3 measured in the drisapersen program did not appear to be inversely correlated to CK. It is uncertain if the inflammatory response due to injection site reactions could be associated with a reduction in CK, although CK reduced by 30-40% in subjects with or without injection site reaction.

- In a 14-day study with gentamicin, CK dropped by 50% in DMD boys (Malik 2010), while dystrophin increased after 6 months of dosing. In another 14-day study the highest drop in CK with gentamicin was after 1 day of dosing (Wagner 2001).



Gentamicin has a short half-life of 2-3 hours, but uncertain is this reduction in one day is mechanistically plausible. CK was assessed at earlier time points in some subjects on drisapersen. The CK reduction appeared to be lower at Week 3 compared to Week 49, but there was a large variability between time points. This is somewhat reassuring given the long half-life of drisapersen. Therefore, it is uncertain to what extent these factors could play a role in reducing serum CK levels and if CK change are essentially caused by improvement in muscle integrity or due to other unknown factors such an increase in metabolism of CK caused by the drug. While some factors could be explained by data, the others remain unknown. In addition, there was no correlation of 6MWD and CK, as in the Phase 3 study. Therefore, given all these caveats, a treatment effect due to reduction in CK is difficult to discern, but a plausible treatment effect cannot be ruled out.

MRI: Consult review of the MRI data conducted by Dr. Daniel Krainak (CDRH Imaging Division) concludes that the data presented in the application are unconvincing of treatment benefit.

Dystrophin:

The utility and caveats of dystrophin measurement in DMD:
Genetic mutation and deficiency of dystrophin leads to DMD in humans. Dystrophin has a structural role in the dystrophin-associated glycoprotein complex as a cytoskeletal stabilization protein and protects muscle fibers against contraction induced damage. Dystrophin also has a signaling role that includes mechanotransduction of forces and localization of proteins. Mutations in the DMD gene disrupt the open reading frame and prevent the full translation of dystrophin. Hence, there appears to

an intrinsic biological reason to measure dystrophin in DMD patients. Drisapersen is designed and targeted to restore the open reading frame with the production of a truncated but functional dystrophin. However, in humans, a quantitative, linear, and direct correlation between restoration of functional dystrophin and treatment benefit in terms of muscle function has not been clearly established (see discussions by Wilton2014 and Lu 2014). Qualitatively, the existence of Becker patients with detectable levels of dystrophin and milder phenotype than Duchenne patients suggests that dystrophin is, at least in part, related to the muscle function. Morandi and others have unsuccessfully attempted to establish this quantitative relationship using BMD cohorts (Morandi 1995).

In the mdx animal model for DMD, dystrophin restoration at levels of ~25-80% of normal have been achieved with antisense oligonucleotides (Gao 2014) or exon-skipping morpholino oligomers (Goyenvalle 2010). In these and other studies, dystrophin restoration was observed along with prevention of dystrophic pathology and restoration of muscle strength in the animal muscles examined.

In humans, some caveats that complicate a clear relationship between dystrophin protein and functional outcome are:

1. The presence of variable levels of trace and revertant fiber dystrophin. The low levels found in DMD also suggest that trace levels of dystrophin are unlikely to limit muscle degeneration.
2. The heterogeneity of the dystrophin between muscle sub-groups (e.g. biceps vs quadriceps) and within the same muscle biopsy.
3. The genotype and specific gene mutation of a BMD or DMD appears to impact basal levels of dystrophin but a systematic study hasn't been presented.
4. Inconsistent or heterogeneous measurement of dystrophin across laboratories that claim a quantitative relationship. Lack of a reference standard and proper control samples also make robust quantitative claims questionable.
5. The severity of the disease as a consequence of the chronic inflammatory environment. Lack of dystrophin also stimulates an inflammatory response that is an important mechanistic driver for the muscle degenerative process over time. With increasing age, the interplay between chronic activation of innate immunity and asynchronous bouts of degeneration/regeneration combine to yield a poorly orchestrated repair response that may itself drive disease progression (Rosenberg 2015). It is possible that the chronic inflammatory environment and repeated muscle damage over time presents a point-of-no-return that cannot be overcome simply based on restoration of extremely low levels of dystrophin.
6. Restoration of truncated dystrophin in DMD patients likely triggers an auto-immune response to the new protein in these patients. Even though these patients have revertant fibers, Flanigan and Mendel have previously published that these patients are not "tolerized" to novel dystrophin production and show dystrophin-specific T-cell immunity that increases with age (Fanigan 2013). In animal models, this was mitigated with administration of anti-inflammatory agents (Villalta 2014 and Rosenberg 2015). How the autoimmune response to the new dystrophin impacts its availability and function within muscle tissue is unclear.

Detection of dystrophin was assessed by exon 51 skipping by RT-PCR, qualitative IFA and WB in Study

DMD114117, DMD114876, DMD114044, DMD114673 and PRO051-01. A small to non-existent dystrophin increase in dystrophin from baseline was observed; however, this increase was not consistent across all the placebo controlled studies. A relatively reasonable assessment of dystrophin increase was only obtained from Study DMD114117. The results across placebo controlled studies and methodologies are summarized below.

Dystrophin mRNA by PCR: The applicant provided a qualitative assessment of dystrophin mRNA by either nested, lab-on-chip, or droplet digital PCR. These methods do not indicate that mRNA was translated into functional protein.

- *Nested RT-PCR:* Nested RT-PCR assessments were qualitative with assessments of visual bands (yes/no). A small increase in exon 51 skipped dystrophin mRNA was observed only in some patients across studies with no consistent trend between treatment groups as summarized below.

Study	Number of subjects/total number analyzed		
	Placebo	6 mg/kg/week	6 mg/kg Inter OR 3 mg/kg/week
Study 114117 (Wk 24)	0/18	2/18	5/17
Study 114876 (Wk 24)	2/16	10/18	10/17
Study 114044 (Wk 48)	56/61	114/125	-

- *The Lab-on-chip capillary electrophoresis PCR:* This method showed some increase compared to baseline but the standard deviations were high. Due to several analytical deficiencies, this quantitation has limited reliability.

Study Treatment	Exon skip (a.u) (mean(SD))	
	Week 0	Week 25, 24 or 48
Study 114117		
Placebo	1.30 (1.01)	0.73 (0.41)
Weekly 6 mg/kg/week	1.29 (2.42)	1.30 (1.50)
Intermittent 6 mg/kg	1.72 (2.38)	2.60 (5.34)
Study 114876		
Placebo	2.01 (1.52)	1.53 (1.20)
Weekly 6 mg/kg/week	2.69 (4.09)	4.44 (3.55)
Weekly 3 mg/kg/week	2.41 (4.38)	4.37 (6.78)
Study 114044		
Placebo		1.45 (1.68)
Weekly 6 mg/kg/week		2.83 (5.21)

Dystrophin Protein by Immunofluorescence:. Immunofluorescence assessments suggest small increases in mean membrane-associated dystrophin intensity in some treated patients from study 114117 but not from studies 114876 or 114044 as summarized below. IFA quantitation of dystrophin has high

background and may increase more than linearly with small changes in dystrophin which could lead to an overestimation of amount of dystrophin compared to WB. The IFA method can suggest protein localization but is less meaningful for protein level quantitation.

Study	Number of subjects/total number analyzed		
	Placebo	6 mg/kg/week	6 mg/kg Inter OR 3mg/kg/week
Study 117 (Wk 24)	1/18	9/15	4/15
Study 876 (Wk 24)	7/12	1/18	5/11
Study 044 (Wk 48)	9/61	9/125	

Dystrophin Protein by Western Blot: Some patients in study 114117 showed a small increase compared to baseline but with very low dystrophin signal compared to healthy samples.

Study	Number of subjects/total number analyzed		
	Placebo	6 mg/kg/week	6 mg/kg Inter OR 3 mg/kg/week
Study 114117 (Wk 24)	0/14	5/17	5/16
Study 114876 (Wk 24)	0/5	0/1	1/5
Study 114044 (Wk 48)	-	-	-

The applicant's WB method was more quantitative than IFA because (1) a serial dilution of healthy tissue sample was used alongside test samples and control samples and (2) a reasonably muscle-specific α-actinin loading control was included.

Open-label studies: The dystrophin increase was unreliable and unimpressive from the open label studies as discussed below:

Study DMD114673: Dystrophin was assessed at Week 24 and Week 72 of this extension study.

- For IFA analysis, at week 24, no reliable estimate of dystrophin expression was obtained due to poor muscle biopsy quality in the 12 subjects. However, 8/12 subjects had additional biopsy at Week 72. Some subjects showed a slight increase (2 to 8%) in mean membrane intensity, while other showed a slight decrease (1 to 9%) at Week 72, leading to no consistent evidence of increase in dystrophin expression.
- For WB analysis, an increase of 21-46% at week 24 over previous time point was observed; however, at week 72 the same patients did not consistently show an increase. Upon request, the applicant clarified that, with the exception of one sample at 1.1% the dystrophin levels observed in this study were all below 1%, which is their lower limit of detection by WB.

Study PRO051-02: Dystrophin expression was evaluated 2 and 7 weeks AFTER a 5 week dosing period in 12 subjects.

- This study does not give reliable estimates of dystrophin. There were no baseline samples in 9/12 subjects. This is the only study where dystrophin expressions have been reported by

the investigator after 5 weeks of dosing with drisapersen.

7.1.3. Subpopulations

Age:

No conclusive evidence of efficacy in any age group can be established from the placebo controlled studies. Age was post-hoc subgroup analysis for studies DMD114117 and DMD114876, but was pre-specified as a subgroup for Study DMD114044. The age groups evaluated were ≤ 7 years and > 7 years, as published data suggest that there are differences in disease progression among these subgroups, but these differences are also dependent on the baseline 6MWD.

McDonald et al and many other experts have shown that *"there is a trend for the 6MWD to improve or be stable over the first 7 years of age and patients who have lower initial 6MWD tend to show greater declines over the course of 48 weeks. Patients ≥7 year of age may also show stable function or even improving function, but they are almost those with higher levels of baseline function (6MWD >350m)"* (Excerpt from McDonald 2013). Please note that there are imbalances in the 6MWD between treatments in some of these age comparisons such that it complicates the interpretation of these age differences in treatment effect.

The age subgroup analyses in the placebo controlled studies are shown in Table 53. Age subgroup analysis was not nominally positive in any study. The age related differences seen in the post-hoc analyses of small phase II studies (DMD114117, DMD114876) are unreliable due to small number of subjects in each group and due to an imbalance in the baseline 6MWD in the treatment and placebo arm within some age comparisons.

Table 53: Age subgroup analyses in placebo controlled studies

Treatment	N	Baseline Mean (SD)	Adjusted Mean Change from Baseline (SE) at Week 48*	Treatment Difference	95% CI
Age ≤7 years at Baseline (Study DMD114044)					
Placebo	29	383 (66)	-25 (11)	21	(-6, 48)
Drisapersen 6 mg/kg/wk	51	368 (65)	-4 (8)		
Age ≤7 years at Baseline (Study DMD114117)					
Placebo	13	409 (40)	-13 (16.54)	38	(-12, 89)
Drisapersen 6 mg/kg/wk	11	413 (62)	25 (18.20)		
Age ≤7 years at Baseline (Study DMD114876)* 24 weeks					
Placebo	6	445 (63)	-14 (21)	31	(-29, 90)
Drisapersen 6 mg/kg/wk	10	385 (60)	17 (17)		
Age >7 years at Baseline (Study DMD114044)					

Placebo	32	316 (101)	- 84 (15)	7	(-29, 43)
Drisapersen 6 mg/kg/wk	74	316 (107)	-77 (11)		
Age >7 years at Baseline (Study DMD114117)					
Placebo	4	386 (57)	-61 (24)	56	(-6, 114)
Drisapersen 6 mg/kg/wk	7	450 (81)	-5 (18)		
Age >7 years at Baseline (Study DMD114876)* 24 weeks					
Placebo	10	399 (48)	- 16(12)	28	(-9, 64)
Drisapersen 6 mg/kg/wk	8	410 (62)	12 (14)		

In study DMD 044, the subjects ≤ 7 years had larger treatment benefit (21 m) than subjects > 7 years (6.9m). The applicant believes that younger subjects may have greater treatment benefit with drisapersen. In this comparison, one 7 year old subject (#1256) on placebo with a baseline 6MWD of 184m could not perform the test due to gait loss after Week 12. This inability to perform the test is not likely to do the lack of response to treatment after Week 12, but more likely to the disease condition of this subject. A treatment difference of 10 m was observed in subject's ≤ 7 years of age after removing this single subject. This further weakens the notion that younger subjects may receive greater treatment benefit.

In addition, pooling the two Phase II studies, which the applicant asserts was a more functional population, the treatment difference over placebo was greater for the older subjects (40m), compared to the younger subjects (27m) at Week 24, further weakening the notion that treatment effect is greater in the younger population.

Pooling the 48 week placebo controlled studies, a larger treatment difference of 24m was observed for the younger population compared to a 7m treatment difference in the older subjects. Pooling the 48 week studies, I also conducted an exploratory post-hoc analysis by age in subjects with Rise from Floor ≤ 7 seconds which is summarized in Table 54. Given the few number of subjects that were >7 years, the interpretation of the data across all ages are not reliable. Nevertheless, the 5-6 year old subjects showed greater treatment difference.

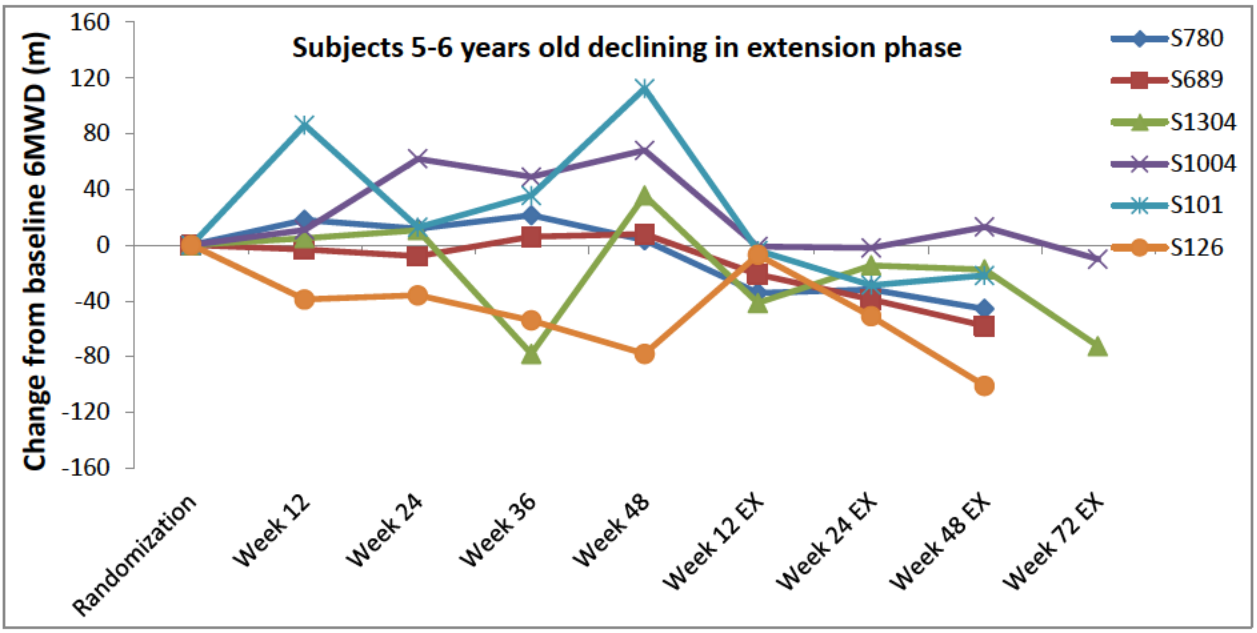
Table 54: Pooled 6MWD analysis by age for the 48 week studies in subjects with Rise from floor ≤7s

Age	Drisapersen N	Placebo N	Mean Treatment Difference
5 years	12	10	67 m
6 years	23	11	28 m
7 years	14	12	12 m
8 years	14	6	2 m
9 years	7	5	31 m
10 years	2	1	-67 m
11 years	2	1	32 m

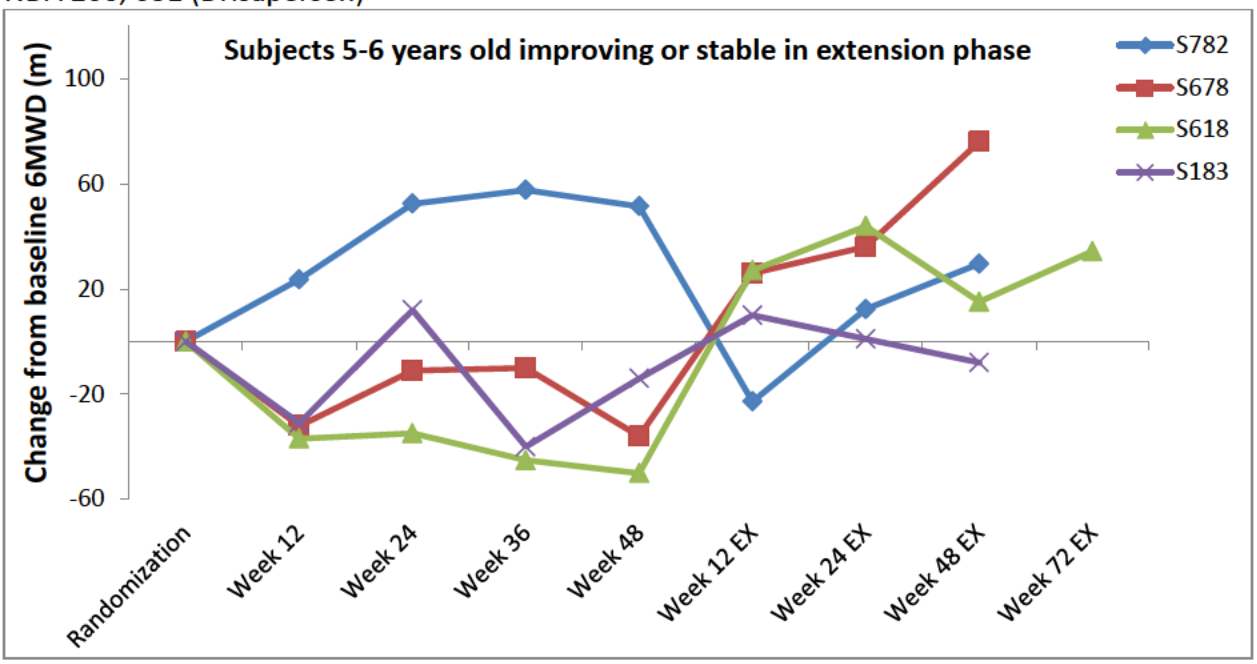
Note: The baseline 6MWD was lower by 8-20m in the drisapersen arm in the ages 5-7 years

Experts have suggested that viable muscle fibers may be required to restore dystrophin and hence would seem logical to start treatment early for a treatment benefit in the long-term. Keeping this hypothesis in mind, I looked at the 6MWD time course in the open label extension phase for the 5-6 year old from Study DMD114044. There were 10 subjects on treatment of the ages 5-6 years that had ≥2 year data from the open label extension phase. Of these 10 subjects, 6 tended to decline in the 2nd year of treatment with continuous 6mg/kg/week drisapersen, 4 tended to improve. The data from a few of these 10 subjects could be considered random noise in the measurement. For ease of visual representation these 6MWD time course of these subjects have been categorized as those improving and declining in the extension phase (Figure 32). These figures suggest that some subjects tend to decline in the 2nd year of treatment with 6mg/kg/week drisapersen. Given the variability in the progression, it is difficult to get an estimate of the time to loss of ambulation in these young subjects.

Figure 32 Two year time course of 6MWD of 5-6 year old subjects from Study DMD114044



Note: EX stands for extension phase



Overall, there is no compelling evidence that the subjects ≤ 7 years of age may benefit treatment with drisapersen, but a plausible biological argument can be logical.

Ethnicity and Race:
There is insufficient data on ethnic and race comparisons for efficacy. A total of 82-95% of the subjects were Not-Hispanic/Latino across the three studies. No interpretable differences can be obtained between ethnic groups. A total of 76% of the subjects were White Caucasian/European in Study DMD114044 and 88% in Studies DMD114117 and DMD114876. Due to the small number of subjects of the non –Caucasians, no interpretable treatment difference based on race can be obtained.

Country:
No reliable conclusions can be drawn with respect to efficacy in different countries. A Total of 23 countries participated in the placebo controlled studies. The number of subjects per treatment group was small in these countries. Only Canada, France, Italy, Germany and United States had more than 15 subjects.

7.1.4. Dose and Dose-Response

An initial loading dose of 6mg/kg drisapersen twice weekly for 3 weeks, followed by maintenance treatment with 6 mg/kg administered weekly is proposed. The loading regimen was evaluated in Study DMD114117, in which a statistical significant difference from placebo was observed for the primary endpoint 6MWD. Given, the long half-life of drisapersen (29 days), it is acceptable to initiate treatment with a loading dose for three weeks, as proposed by the Applicant.

6 mg/kg was considered to be the maximum tolerated dose by Applicant due to signs of potential subclinical nephrotoxicity (mild proteinuria) in the extension study DMD114673 after 6 months of

treatment and due to preclinical pro-inflammatory findings (including the recent preliminary data from the 39 week monkey study). Drisapersen doses 0.5, 2, 4 and 6 mg/kg were evaluated in a 5 week proof of concept Study PRO-051. Due to the lack of significant safety findings and a pharmacodynamics effect (increase in dystrophin expression) with 5 weeks of dosing, the 6 mg/kg/week dose was given the open label extension Study DMD114673. A single dose of 9 mg/kg administered to 3 non-ambulant subjects was associated with renal toxicity and inflammatory reactions and self-limiting pyrexia and flu-like symptoms in all subjects. Doses higher than 6mg/kg/week were not evaluated in any other study.

A lower 3 mg/kg dose was evaluated in Study DMD114876 in only 18 subjects. In this study:

- 6 mg/kg/week was superior than placebo (27m)
- 3 mg/kg/week was worse than placebo (-9 m)

Given the variability in the assessment of 6MWD, this difference from placebo is not substantial and could considered as indistinguishable from placebo at Week 24. The sample size of this study is small, hence difficult to conclude that 3 mg/kg/week as an ineffective dose. No clear dose-response was established.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

Pharmacokinetic studies have shown that drisapersen concentrations reach steady state at 24-36 weeks and also likely the time it would take for dystrophin to accumulate in the muscles. None of the placebo controlled studies have shown any dystrophin expression at Week 12, but an exploratory published 5 week study showed an increase in dystrophin after 5 weeks of dosing. In many subjects a change from baseline in 6MWD of similar magnitude was observed both at Week 13 and Week 24. This could be due to the variability in the assessment of 6MWD.

The applicant asserts that there was maintenance of effect after further 24 weeks off treatment. In Study DMD114876, in which treatment was administered for only 24 weeks, change from baseline in 6MWD at Week 24 was 16 m and 15 m at Week 48, after a drug free period. This would suggest that treatment effect is maintained. Given the turnover half-life of dystrophin this may be physiologically possible as well. In this study the treatment difference from also remained similar (27m) at Week 24 and 48. This is because the placebo group also did not decline in the 48 week period. Similar treatment effect was also observed at Week 12, but not certain if the effect at Week 12 is due to increase in dystrophin as no dystrophin was measurable at week 12 in any study. Therefore the maintenance of change from baseline in the 6MWD at Week 48 appears less convincing of a persistence of effect from this study.

The evidence for durability of response is unclear. In Study DMD114117, a mean change from baseline in 6MWD was 31 m at Week 24 and 11 m at Week 48, suggesting a decline in 6MWD of about 20 m. A treatment difference from placebo of 35 m was observed on both Week 24 and Week 48. This probably was due to a decline in the placebo group of about 20 m in this study at Week 48, driven by a few subjects in the study.

The applicant asserts that a difference of ~30 m was observed in subjects who received continuous 6

mg/kg/week for 96 weeks in the extension study of DMD114044 compared to those subjects that received placebo in the parent study for 48 weeks followed by 48 weeks of continuous 6 mg/kg/week regimen. The sample size was reduced to almost 50% of the parent study in each arm; hence the observed difference of ~30 m is uninterpretable, even though it is plausible.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

Drisapersen could be used in the ambulant patients with exon-51 skip amenable DMD, if efficacy were to be established. Effectiveness of drisapersen in non-ambulant patients has not been evaluated. Postmarketting considerations are premature at this time.

7.2.2. Other Relevant Benefits

There are no other relevant benefits at this time.

7.3. Integrated Assessment of Effectiveness

In this section, I discuss the various options of regulatory pathways for drisapersen.

Drisapersen development program has 3 adequate placebo controlled studies with a single primary endpoint and several secondary clinical endpoints.

There is no substantial evidence of efficacy for drisapersen from the adequate and well controlled studies based on a clinical endpoint, change from baseline 6MWD.

There was a statistically significant treatment difference for drisapersen 6 mg/kg/week over placebo (p=0.01) at week 25 for the primary endpoint change from baseline 6MWD in only one small Phase 2 Study DMD114117. The change from baseline in 6MWD observed at Week 25 does not appear sustained at Week 49. An intermittent regimen of the same 6mg/kg dose with identical plasma exposure showed no statistically significant (p=0.80) difference over placebo in this study. The known and unknown biases from this study such as unblinding due to injection site skin reactions and baseline imbalances in prognostic factors due to chance alone could be mitigated if these findings are replicated in independent studies. It is disappointing that there is no independent substantiation of these results from the second Phase 2 Study DMD114876 (p=0.07) and the large Phase 3 DMD114044 (p=0.42) to rule out the possibility of a false positive finding due to chance alone. Removing one placebo subject from the analysis of the Phase 2 Study DMD114876 because the subject was unblinded increased the p-value to 0.21, further weakening the confidence in the evidence towards efficacy from Study DMD114117. Applicant's argument of a more functionally impaired population of the Phase 3 study DMD114044 contributing to a lack of treatment response was not substantiated by a FDA post-hoc analysis of subjects with similar baseline age, 6MWD and rise from floor time as in the Phase 2 studies. There was no statistically significant treatment difference (p=0.71) or even a larger numeric treatment

difference in this subgroup of patients, suggesting that the disease severity of the subjects was not the reason for the negative results from Study DMD114044.

Although a numeric advantage for drisapersen over placebo was observed in the three placebo controlled studies, a precise estimate of possible effect size cannot be established for drisapersen. An aggregate of the data across studies and all post-hoc analyses suggest that if it were to be concluded that the result was due to drug, there was a numerical advantage with drisapersen of approximate 10-20 m over placebo over 24-48 weeks. The clinical meaningfulness of this short term numeric advantage with drisapersen in the overall prognosis remains uncertain.

A number of secondary endpoints were assessed without control for multiplicity. None of the secondary endpoints were nominally positive in any study. Secondary endpoints such as Timed Function Tests (rise from floor, 10m walk/run, 4-stair climb/ascent –descent) and NSAA are also measures of lower limb strength like the 6MWD and are highly correlated to each other. These secondary endpoints were in the same direction as the primary endpoint in only Study DMD114117. There were no consistent trends in favor of drisapersen in other studies. The differences in the Timed Function Tests were mostly <1 second between treatment and placebo in all three studies. Muscle strength measure by myometry and pulmonary function tests did not favor drisapersen. The changes were small across treatment groups. These secondary endpoints analyses do not contribute to the assessment of efficacy.

Even if one were to consider the results of Study DMD114117 bereft of uncertainties, there is no independent substantiation of these findings. A single study approval could be argued for a rare disease with no approved treatments. Single study approvals are generally limited to situations in which the study has demonstrated a clinically meaningful effect on mortality or irreversible morbidity and in which a second trail would be ethically impossible. For this application, we have 2 other adequate controlled studies which cannot be ignored and the endpoint is not mortality or irreversible morbidity. In addition, the study was smaller than a large well powered study that failed to show effectiveness. Given the above concerns from the placebo controlled studies, I do not recommend standard full approval of drisapersen in the treatment of exon 51-skip amenable DMD.

The law under 21CFR 314.500 further provides the regulations for approval under Subpart H-Accelerated approval of new drugs for serious and life threatening disease. DMD is a severe disease in which progressive loss of muscles lead to loss of ambulation, respiratory and cardiac complications and ultimately death. There are no approved treatments of DMD in the United States.

Under Subpart H, approval can be based on either on a “surrogate endpoint” that is reasonably likely based on epidemiologic, therapeutic, pathophysiologic or other evidence to predict clinical benefit at some later time OR on an “intermediate clinical endpoint” that can be measured earlier than an effect on irreversible morbidity or mortality that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit.

I will first consider 6MWD as an “intermediate clinical endpoint”. 6MWD is a clinically meaningful

endpoint in DMD as it is a measure of how a patient functions. It measures how much a subject can walk (in meters) in a fixed time of 6 minutes. While being able to walk more is certainly meaningful in the day-to day activities of the patient, an improvement in measure of a distance could predict an effect on irreversible morbidity or mortality, which is time to loss of ambulation or death, i.e. could affect the ultimate rate of decline. If we were to consider 6MWD as an intermediate clinical endpoint, it would be on the basis of the short-term benefit of walking more reasonably likely to have an effect on the rate of decline of walking performance and thus influence the time to loss of ambulation. Drugs granted accelerated approval MUST meet the same statutory standards of effectiveness and safety as those granted traditional approval. As discussed in the previous paragraphs, the clinical evidence of efficacy for drisapersen does not meet the statutory standard and remains inconclusive based on 6MWD and other clinical secondary endpoints. An aggregate of the data across studies and all post-hoc analyses suggest a relatively short-term numerical advantage with drisapersen of approximately 10-20m over placebo. These differences were not statistically significant, hence no persuasive treatment effect size can established between drisapersen and placebo. Based on natural history studies in DMD, a 10-20m treatment difference between drisapersen and placebo is also not likely to have a large effect on delaying the time to loss of ambulation (Natural history studies have suggested decline in 6MWD of 22-58 m in a year). The open label studies in the application, though not completely interpretable, do not suggest that the rate of decline in the walking performance was different from that of natural history. Hence, based on the unpersuasive results of 6MWD from studies presented in this application, it is uncertain if 6MWD can serve as an intermediate clinical endpoint reasonably likely to predict an effect on irreversible morbidity for this application.

Therefore, the threshold for accelerated approval based on 6MWD as an intermediate clinical endpoint reasonable likely to predict benefit on time to loss of ambulation or the rate of decline appears unmet.

Lastly, I will discuss the regulatory pathway of accelerated approval based on a surrogate endpoint reasonable likely to predict clinical benefit. Creatine kinase, a marker of muscle cell integrity at a molecular level could serve as a surrogate endpoint reasonably likely to predict clinical benefit. CK was reduced by 30-40% across the three studies based on percent change from baseline with nominal p-values of 0.08, 0.53 and <0.001 for the Studies DMD114117, DMD 114876 and DMD114044 respectively, suggesting a plausible improvement in muscle cell integrity. While the reduction CK was consistent across studies, the effect of confounders such as inactivity, reduced muscle mass, steroids use and inflammatory processes cannot be completely understood from the data. There was obviously no correlation of reduced CK to the clinical endpoint 6MWD based on the studies in the Application. A statistical significant ($p<0.001$) reduction in CK was observed despite of no difference in walking ability between drisapersen and placebo ($p=0.42$). Given this, the clinical meaningfulness of the observed reduction in CK is uncertain from the studies in this application. Hence, the reasonably likelihood of a reduction in serum creatine kinase to predict a clinical benefit in function or time to loss of ambulation appears uncertain. An increase in dystrophin protein expression could reflect biological activity and can be considered a surrogate endpoint. It is disappointing that the dystrophin protein expression data were equivocal. The changes in dystrophin were minimal and reliable only in one study.

Therefore, the threshold for accelerated approval based on creatine kinase or dystrophin as a

surrogate endpoint reasonable likely to predict clinical benefit of drisapersen of this application appears unmet as well.

One can argue a numerical advantage on the subjective endpoint 6MWD and on an objective endpoint such as CK in favor of drisapersen in all studies is suggestive that drisapersen is better than placebo. Although, these two together also do not meet the threshold for being reasonably likely to predict an effect on irreversible morbidity or mortality.

The development program for drisapersen is extensive for a rare disease and exemplary. It is very disappointing that that both clinical and biomarker data for drisapersen are inconclusive at this time.

8 Review of Safety

Safety Review Approach

The safety of drisapersen is reviewed by Dr. Evelyn Mentari, MD in a separate review.

9 Advisory Committee Meeting and Other External Consultations

An Advisory Committee Meeting is scheduled for November 24th, 2015.

10 Labeling Recommendations

Labeling recommendations are deferred until Advisory Committee meeting.

11 Risk Evaluation and Mitigation Strategies (REMS)

REMS are not proposed for this application. The reader is referred to Dr. Mentari's safety review.

12 Postmarketing Requirements and Commitments

Postmarketting requirements are deferred until Advisory Committee meeting.

13 Appendices

13.1. References

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13.2. Financial Disclosure

Covered Studies: 3

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 78		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0 Note: There are 33 sub-investigators whose financial disclosure information could not be obtained despite due diligence efforts by the sponsor. These sub-investigators could not be located.		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: NA Significant payments of other sorts: NA Proprietary interest in the product tested held by investigator: NA Significant equity interest held by investigator in S Sponsor of covered study: NA		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Appendix A

North Star Ambulatory Assessment Scale

Activity	2	1	0	Comments
1. Stand	Stands upright, still and symmetrically, without compensation (with heels flat and legs in neutral) for minimum count of 3 seconds	Stands still but with some degree of compensation (e.g. on toes or with legs abducted or with bottom stuck out) for minimum count of 3 seconds	Cannot stand still or independently, needs support (even minimal)	
2. Walk	Walks with heel-toe or flat-footed gait pattern	Persistent or habitual toe walker, unable to heel-toe consistently	Loss of independent ambulation – may use KAFOs or walk short distances with assistance	
3. Stand up from chair	Keeping arms folded Starting position 90º hips and knees, feet on floor/supported on a box step.	With help from thighs or push on chair or prone turn	Unable	
4. Stand on one leg - right	Able to stand in a relaxed manner (no fixation) for count of 3 seconds	Stands but either momentarily or needs a lot of fixation e.g. by knees tightly adducted or other trick	Unable	
5. Stand on one leg – left	Able to stand in a relaxed manner (no fixation) for count of 3 seconds	Stands but either momentarily or needs a lot of fixation e.g. by knees tightly adducted or other trick	Unable	
6. Climb box step – right	Faces step – no support needed	Goes up sideways or needs support	Unable	
7. Climb box step – left	Faces step – no support needed	Goes up sideways or needs support	Unable	
8. Descend box step -right	Faces forward, climbs down controlling weight bearing leg. No support needed	Sideways, skips down or needs support	Unable	
9. Descend box step –left	Faces forward, climbs down controlling weight bearing leg. No support needed	Sideways, skips down or needs support	Unable	
10. Gets to sitting	Starts in supine – may use one hand to assist	Self assistance e.g. – pulls on legs or uses head-on-hands or head flexed to floor	Unable	

Activity	2	1	0	Comments
11. Rise from floor	From supine – no evidence of Gowers' manoeuvre*	Gowers' evident	(a) NEEDS to use external support object e.g. chair OR (b) Unable	Time (00.0s)
12. Lifts head	In supine, head must be lifted in mid-line. Chin moves towards chest	Head is lifted but through side flexion or with no neck flexion	Unable	
13. Stands on heels	Both feet at the same time, clearly standing on heels only (acceptable to move a few steps to keep balance) for count of 3	Flexes hip and only raises forefoot	Unable	
14. Jump	Both feet at the same time, clear the ground simultaneously	One foot after the other (skip)	Unable	
15. Hop right leg	Clears forefoot and heel off floor	Able bend knee and raise heel, no floor clearance	Unable	
16. Hop left leg	Clears forefoot and heel off floor	Able bend knee and raise heel, no floor clearance	Unable	
17. Run (10m)	Both feet off the ground (no double stance phase during running)	'Duchenne jog'	Walk	Time (00.0s).....
				TOTAL= /34

Grading for Timed Function Tests

Grading of rising from floor (supine to stand)

1. Unable to stand from supine, even with use of a chair.
2. Assisted Gower's – requires furniture for assist in arising from supine to full upright posture.
3. Full Gowers – rolls over, stands up with both hands "climbing up" the legs to achieve full upright posture.
4. Half Gowers – rolls over, stands up with one hand support on leg.
5. Rolls to the side and/or stands up with hand one or both hands on the floor to start to rise but does not touch legs.
6. Stands up without rolling over or using hands.

Grading of 10 m walk/run test

1. Unable to walk independently.
2. Unable to walk independently, but can walk with full leg calipers (KAFOs) or with support from a person.
3. Highly adapted wide based lordotic gait. Cannot increase walking speed.
4. Moderately adapted gait. Can pick up speed but cannot run.
5. Able to pick up speed, but runs with a double stance phase, i.e. cannot achieve both feet off the ground.
6. Runs and gets off both feet off the ground (with no double stance phase).

Grading of 4-stair climb

1. Unable to climb 4 standard stairs
2. Climbs 4 standard stairs "marking time" (climbs one foot at a time, with both feet on a step before moving to next step). Uses both arms on one or both handrails.
3. Climbs 4 standard stairs "marking time" (climbs one foot at a time, with both feet on a step before moving to next step). Using one arm on one handrail.
4. Climbs 4 standard stairs "marking time" (climbs one foot at a time, with both feet on a step before moving to next step). Not needing handrail.
5. Climbs 4 standard stairs alternating feet, needs handrail for support.
6. Climbs 4 standard stairs alternating feet, not needing handrail support.

Grading of 4-stair descend

1. Unable to descend 4 standard stairs.
2. Descends 4 standard stairs "marking time" (descends one foot at a time, with both feet on a step before moving to next step). Requires both arms on one or both handrails.
3. Descends 4 standard stairs "marking time" (descends one foot at a time, with both feet on a step before moving to next step). Requires one arm on one handrail.
4. Descends 4 standard stairs "marking time" (descends one foot at a time, with both feet on a step before moving to next step). Not needing handrail.
5. Descends 4 standard stairs alternating feet in both directions, needs handrail for support.
6. Descends 4 standard stairs alternating feet, not needing handrail support.

Appendix B [Additional Dystrophin bioassay-related reviewer comments]

RT-PCR measurement of dystrophin exon 51-skipped mRNA:

While the exact cause for these spontaneous exon skipping is unknown, alternative splicing events and skip frame-shifting that restore the open reading frame (ORF) for dystrophin might result in the spontaneous internally-deleted dystrophin in these fibers. No comprehensive study in boys with DMD has been conducted to characterize the extent of baseline revertant dystrophin but smaller studies have suggested that at least 50-62% of DMD cases show some baseline dystrophin-positive fibers and that the percentage of revertants or trace dystrophin fibers within these samples ranged from 0.01 to 25%. The reason for these baseline exon skipped mRNA and their correlation to protein levels after treatment has not yet been clearly defined in published studies. Emerging literature suggests that the *stability* of the transcript (skipped mRNA) is an important factor for determining ultimate dystrophin protein expression, rather than the *amount* of transcript. As their proposed mechanism of action, exon 51 skipping therapies should result in an increase in overall percentage of fibers with stable exon 51 skipped products when compared to a patient-matched baseline sample from the same muscle sub-group. The data is not adequate to demonstrate an increase in skipped product because it is a qualitative assay with no internal controls for reference. An intensity measurement of the PCR fragment(s) at multiple time-points could add some confidence, as attempted by the applicant with the nested RT-PCR approach.

The stability of the exon skipped transcript detected is also not apparent from the nested/lab-on-chip analysis. Any proposed correlation between dystrophin mRNA and protein levels is complicated by the known instability of the mRNA. Spitali et al (2013) have reported that Becker patients and mdx mice show significant transcript instability that obscures a clear correlation between transcript and protein levels. Anthony et al (2014) reported transcript instability in DMD patient samples with out-of-frame deletions compared to in-frame deletions. They suggest that measuring transcript stability by covering multiple exon junctions for dystrophin might indicate stability, which may be more important for predicting protein levels than measuring amounts of transcript. By using a nested PCR approach, the applicant may have hypothetically enhanced specificity for the target sequences on dystrophin but their exact primers were not described or whether their method captures transcript stability. Specifically, the applicant did not use multiple primers to cover additional regions of the target dystrophin skipped product to be able to predict stability of the transcript, as suggested by the literature cited above, which may be a better predictor of pharmacodynamic activity. While their lab-on-chip capillary electrophoresis/nested PCR method is a reasonable qualitative method for detecting dystrophin transcript, it may not provide the most accurate representation of exon skip that would be predictive of dystrophin protein expression. Additionally, no reference standard or calibration curve was used so it is not possible to interpret the applicant's data as reflective of absolute copy numbers of dystrophin transcript.

Assay cut-offs and scoring approach for the IFA and WB methods:

According to the applicant, for IFA, an increase in dystrophin was defined as an increase in mean membrane intensity of more than 4% at week 25 compared to pre-treatment biopsy. A strong increase in dystrophin was defined an increase in dystrophin intensity by ≥9% for the mean or ≥4% for the mean accompanied by an increase of ≥15% for the 10th quartile of most intensive pixels and confirmed by visual inspection of the images. A decrease was ≤ –4% for the mean membrane intensity. For WB, an increase was defined as a >30% increase in densitometric value of the ~427 kDa dystrophin band (post treatment –pre-treatment/pre-treatment)*100.

The 4% assay cutoff for an IFA score of "increase" and >9% for "strong increase" appears reasonable from a purely analytical standpoint because the inter- and intra-assay variability observed by the applicant is between 2-5% for this immunofluoresence assay. The Applicant also cited an mdx mouse model study where motor function was improved when levels of dystrophin were >4% compared to healthy control muscle. However, no

correlative human endpoint data (e.g. muscle function or DAPC protein co-localization) has been presented to support the biological significance of this scoring. Therefore, it cannot be concluded that the applicant's assay assay cut-offs are biologically meaningful.

Correlation between IFA, WB, and RT-PCR methods:
A clear, consistent, and positive correlation between all three assays - IFA, WB, and Exon skip -has not been established by the Applicant or published literature in the field using appropriate positive/negative controls (e.g. with BMD, DMD, healthy samples in the linear range). As presented by the applicant, the WB data is likely to be most reliable because a serial dilution with a healthy positive control was used for comparison and pre-treatment and post-treatment samples were run on the same gel in most instances. The IFA can suggest protein localization but is likely to be less meaningful for protein level quantitation.

Taylor et al have reported a correlation between immunofluorescence-based intensity ratios of dystrophin/spectrin and dystrophin protein levels measured by Western blotting and normalized to actin. In the article, data have been presented, suggesting a strong correlation between Western blotting and IFA (Anthony 2014 and Kevin Flanagin, Nationwide Children's Hospital, Columbus, OH, at the FDA-NIH Dystrophin Workshop 2015). However, the data presented also had an inter-laboratory variability CV of 22-67% for IFA, which lowers the confidence in the quantitative abilities of IFA and reproducibility of the findings.

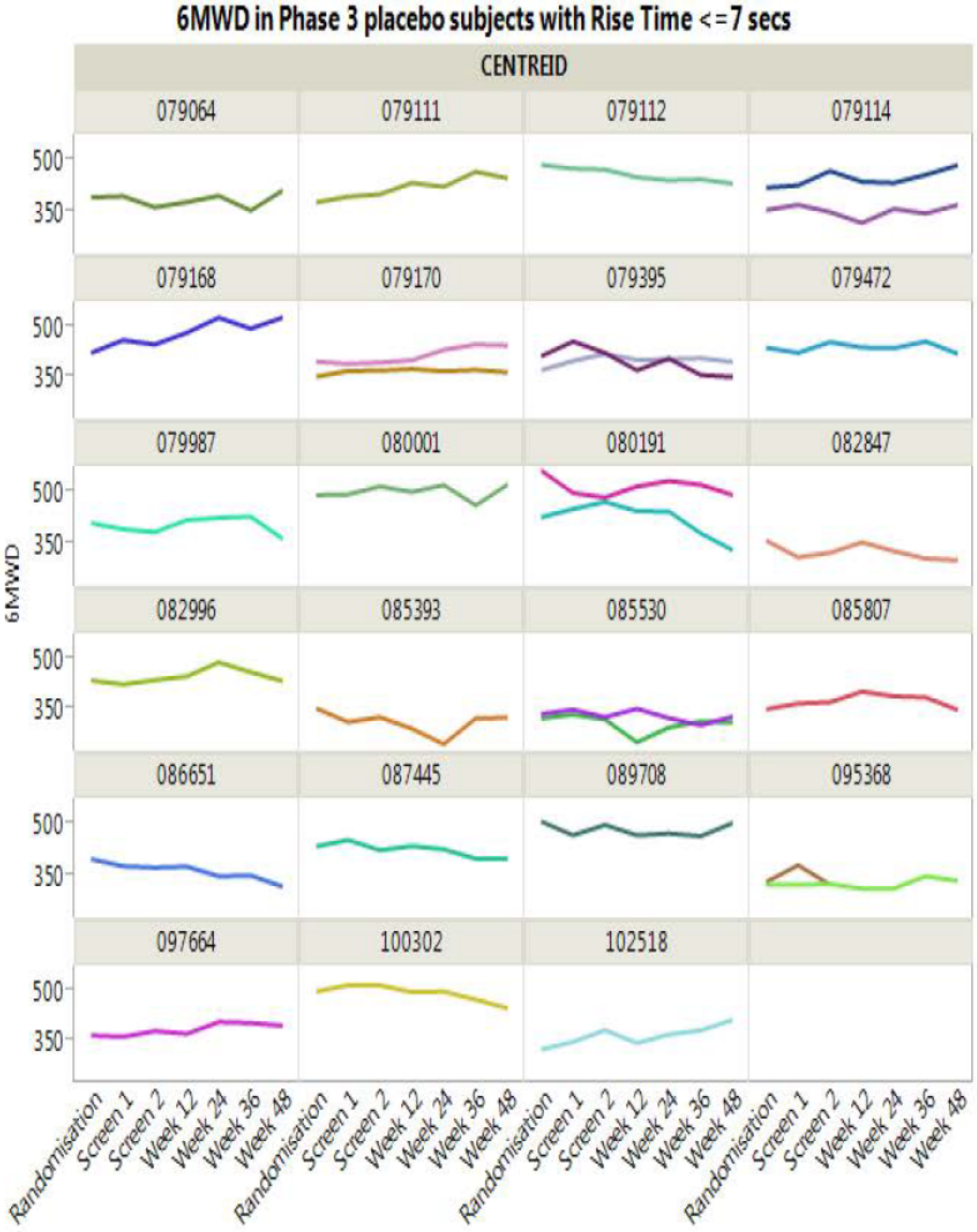
The correlation between IFA and WB methodologies likely depends on several factors including, but not limited to, (1) the differences in the basic assay methodologies (e.g. single cell-based microscopy versus homogenized lysate-based WB), (2) the antibodies used, the epitopes being targeted, as well as the exposure of those dystrophin epitopes to the antibodies in its intracellular or lysate state (3) the staining controls used (e.g. spectrin versus actin), (4) the measurement controls used (e.g. a negative DMD or positive healthy sample), (5) operator bias in the absence of automated image capture or analyses, (6) distribution and localization of dystrophin within the muscle fiber, (7) heterogeneity in the levels of revertant dystrophin between and within individual DMD patients, (8) sensitivity of the detection systems (e.g. fluorescence-tagged antibodies or densitometer instrument used), and (9) the limits of detection and quantitation for either methods. While it may be challenging to establish a strong quantitative correlation between WB and IFA, the protein levels observed the two methods for an appropriately designed experiment should trend in the same direction.

Additional comments on the deficiencies with the IFA methodology used in study 114876:
The applicant states that the inter-assay reproducibility of their IFA assay between experiments for placebo and drisapersen-treated subjects combined was 5% and ranged between 0-16% for the study. It is not clear if the mean values reported in Table 26 that are below 5% represent biologically-relevant responses or expected assay variability. There also appear to be several critical deficiencies in the applicant's analytical approach that preclude an interpretable assessment of dystrophin increase.

The Applicant states that a large change in spectrin (>20%) was observed between Week 24 and baseline biopsies, it is not clear whether and how this impacted dystrophin intensity measurements. However, it may suggest that either spectrin or the way spectrin was analyzed was not suitable for the intended purpose of being a muscle fiber co-stain. This could have been addressed by conducting adequate assay validation prior to clinical sample testing.

The number of subjects with sufficient quality, size, and muscle fiber content for each group was low (12, 11, and 13 for placebo, Week 24-3 mg/kg, and wk24- 6 mg/kg).

Appendix C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087445
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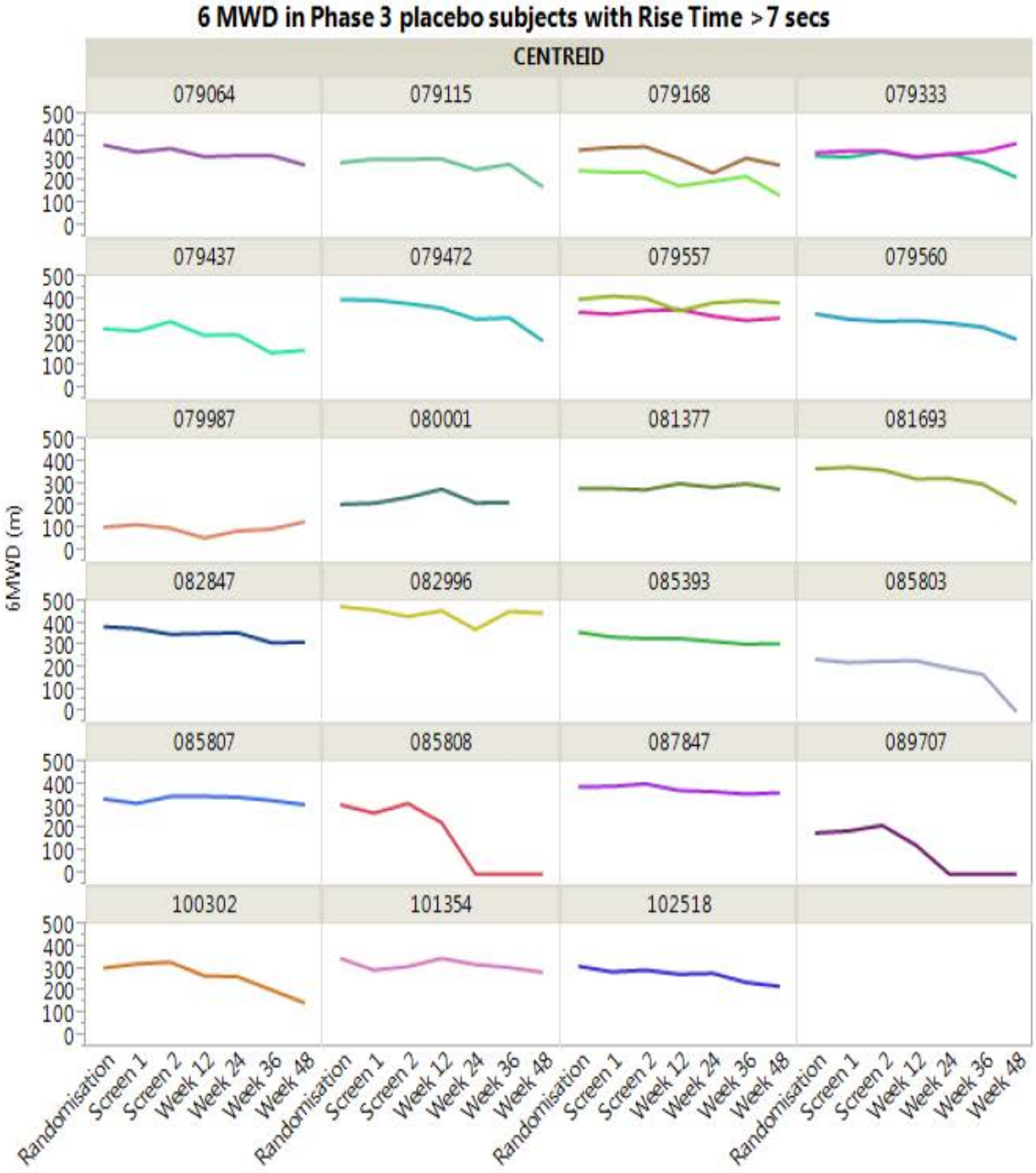
Randomisation
Screen 1
Screen 2
Week 12
Week 24
Week 36
Week 48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100302
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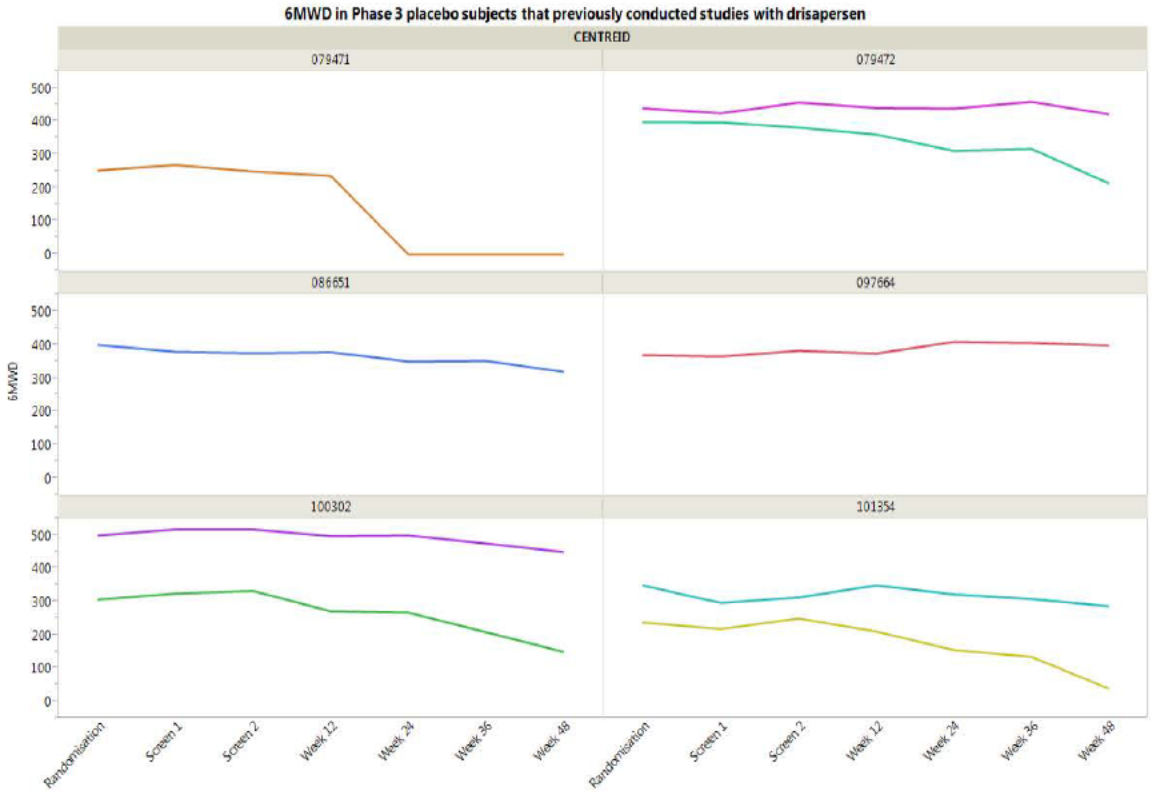
Screen 2
Week 12
Week 24
Week 36
Week 48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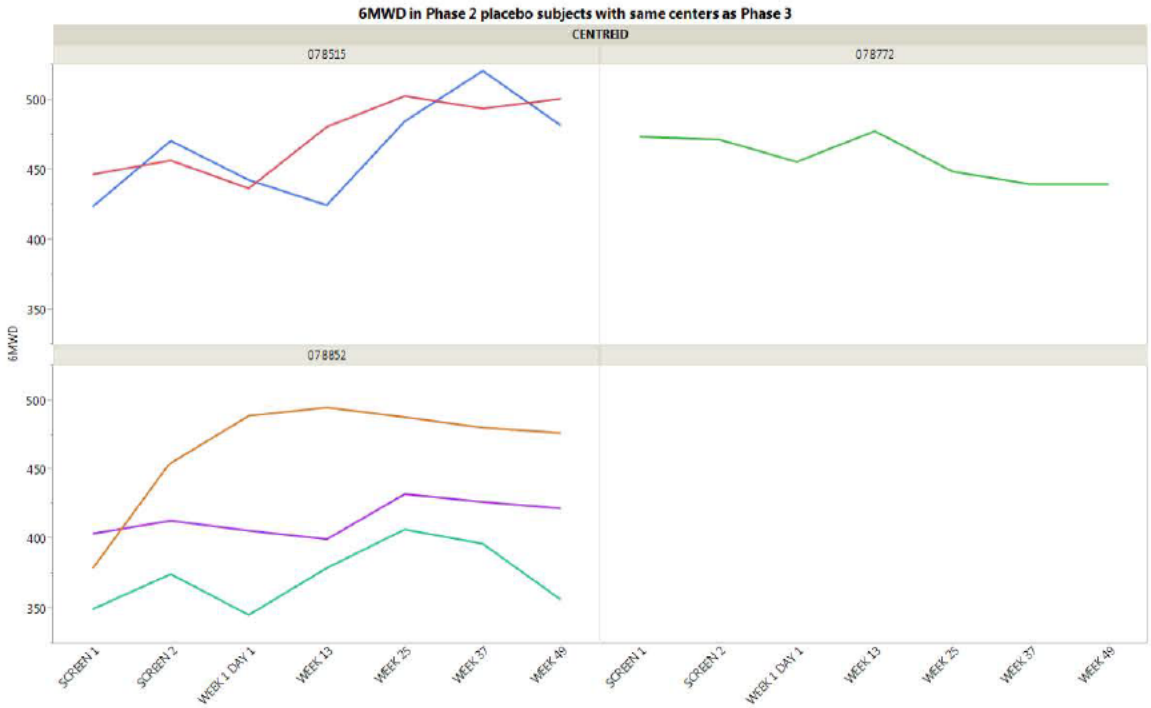
Week 24
Week 36
Week 48


6MWD in Phase 2 placebo subjects with same centers as Phase 3
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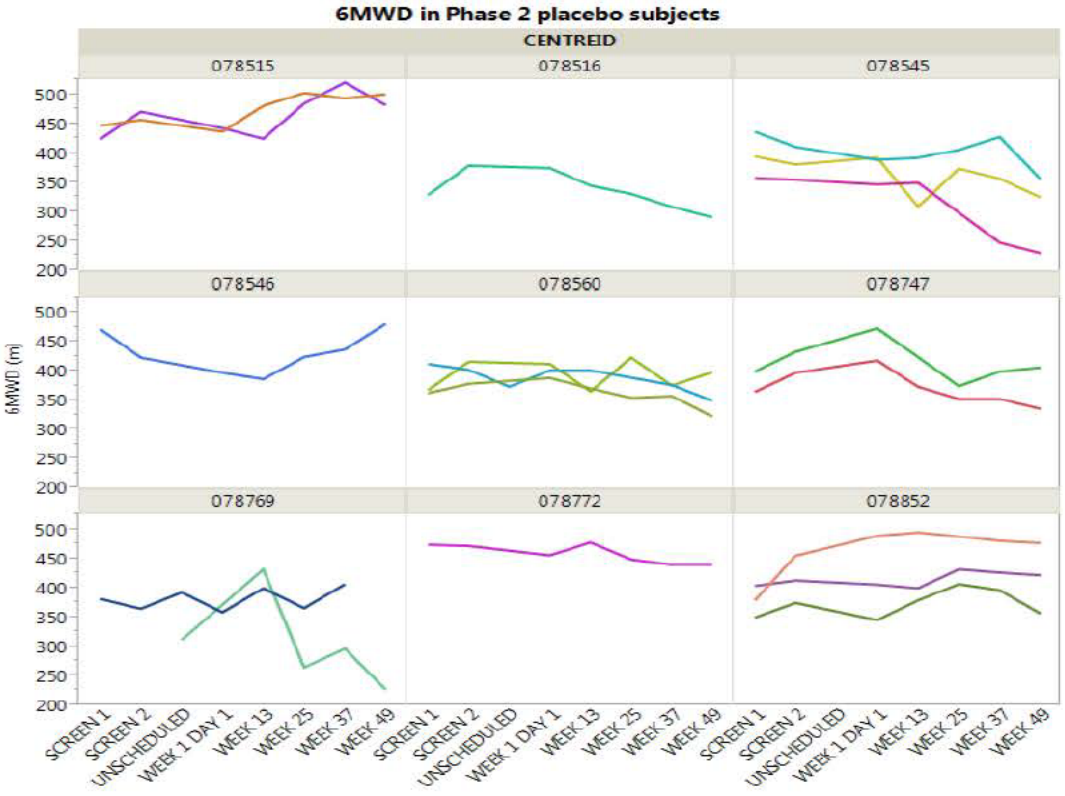
SCREEN 1
SCREEN 2
WEEK 1 DAY 1
WEEK 13
WEEK 25
WEEK 37
WEEK 49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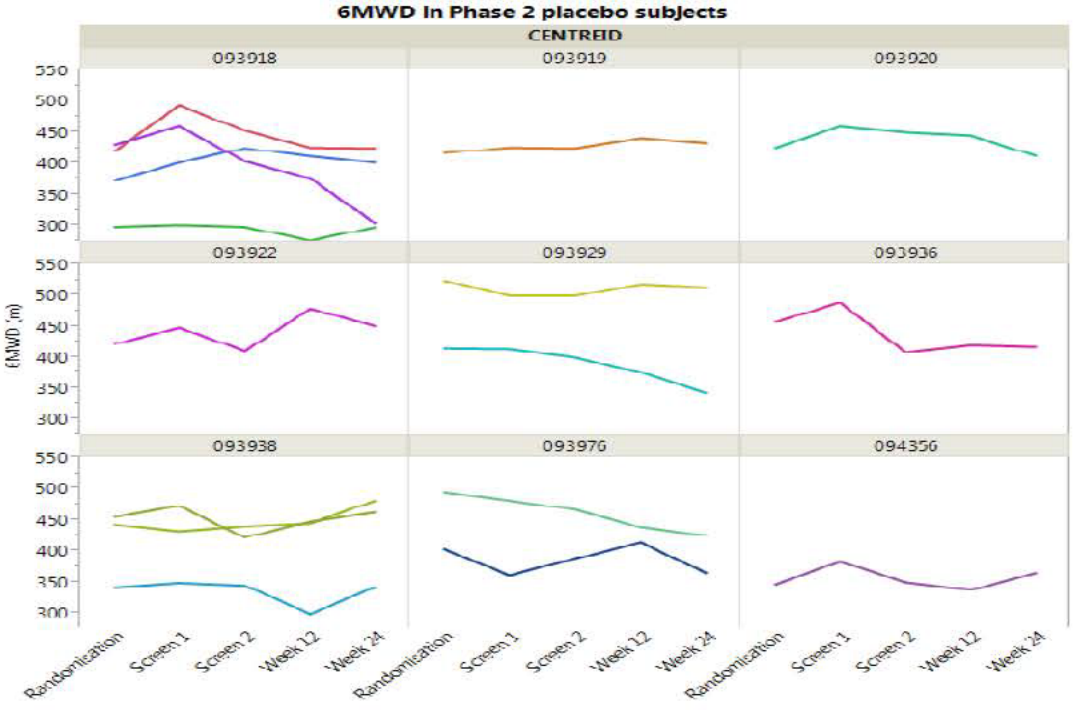
SCREEN 2
UNSCHEDULED
WEEK 1 DAY 1
WEEK 13
WEEK 25
WEEK 37
WEEK 49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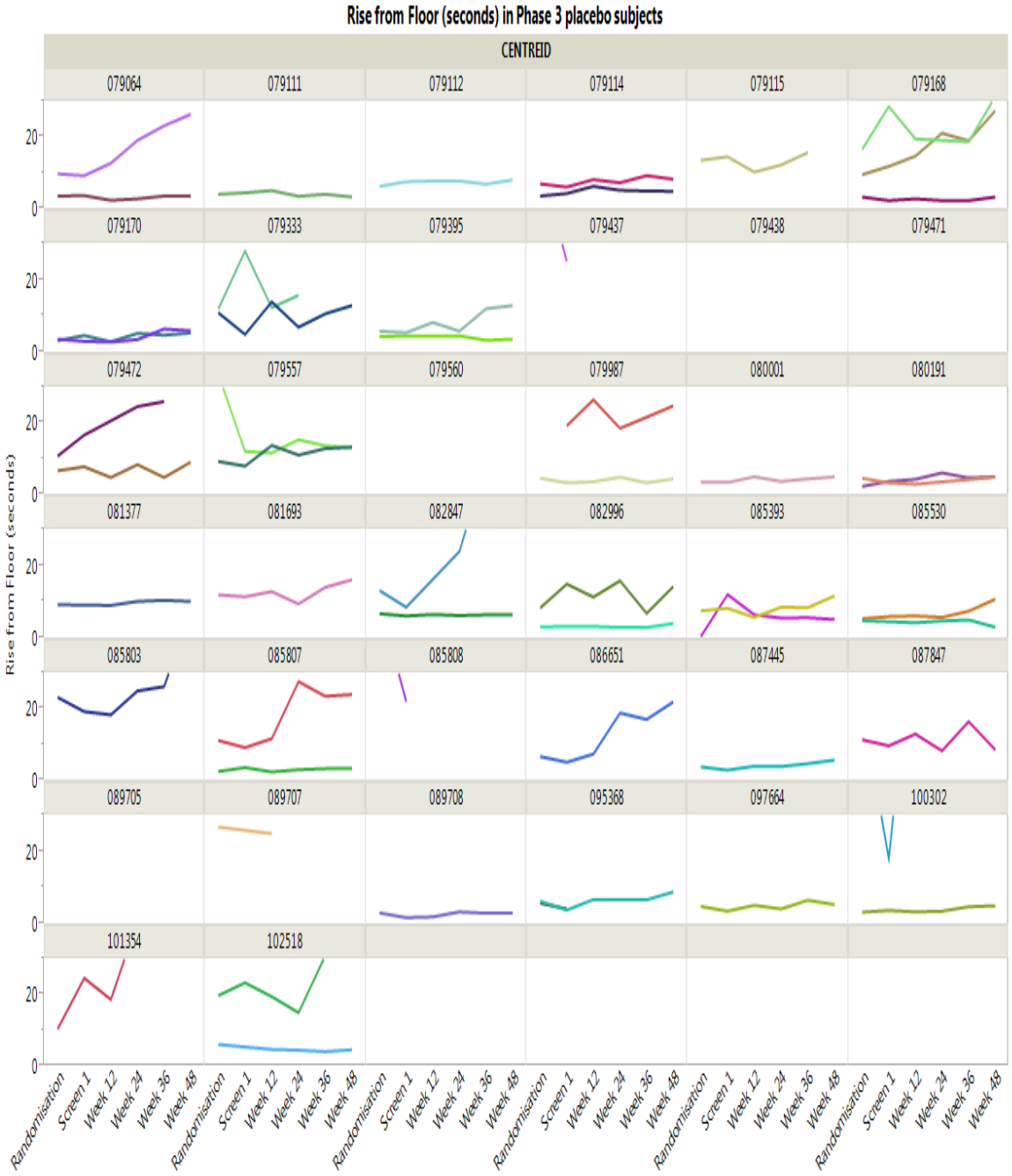
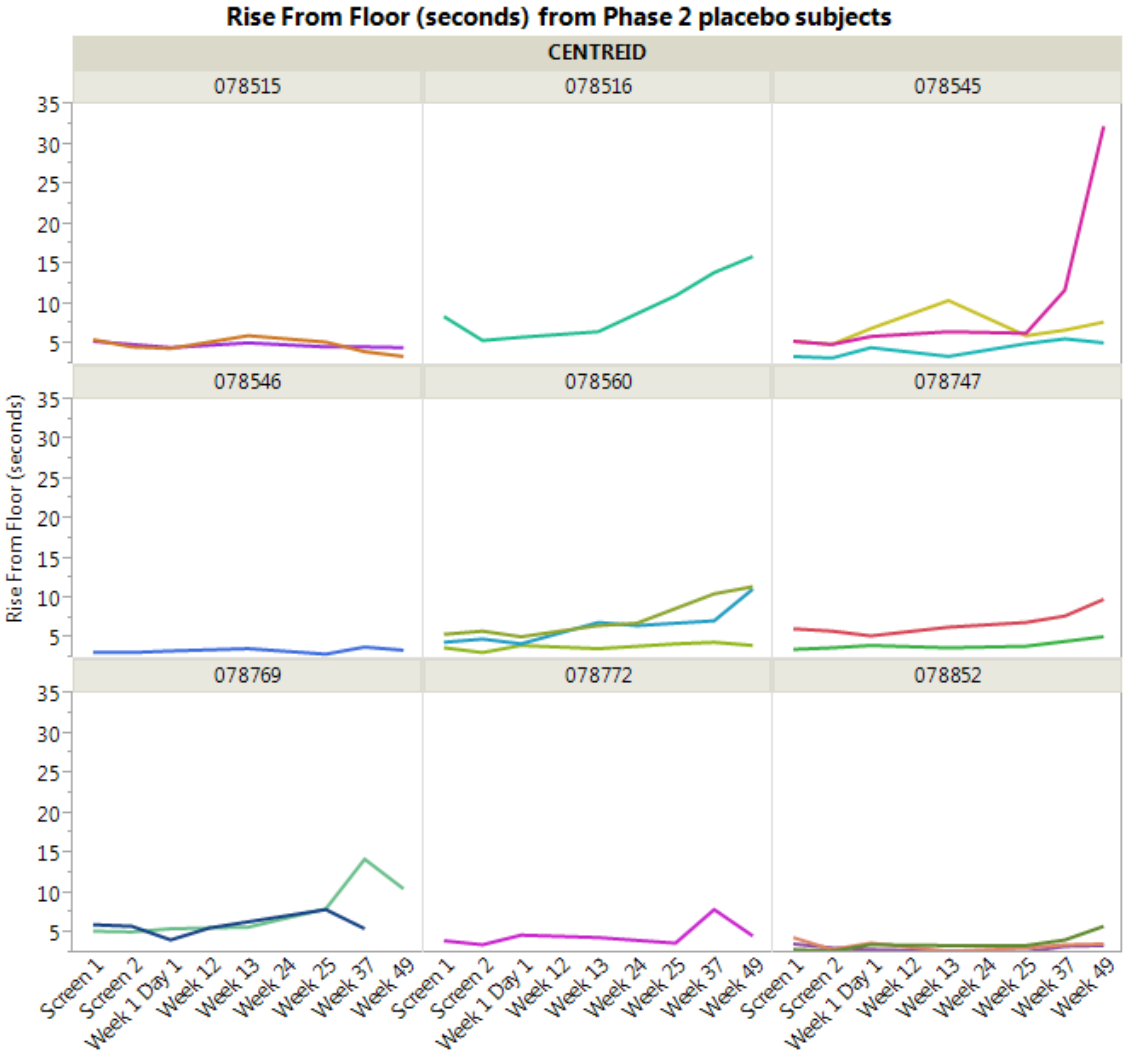
Screen 2
Week 12
Week 24



Note: The Y-axis has been truncated to 30 seconds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Rise From Floor (seconds)
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15
10
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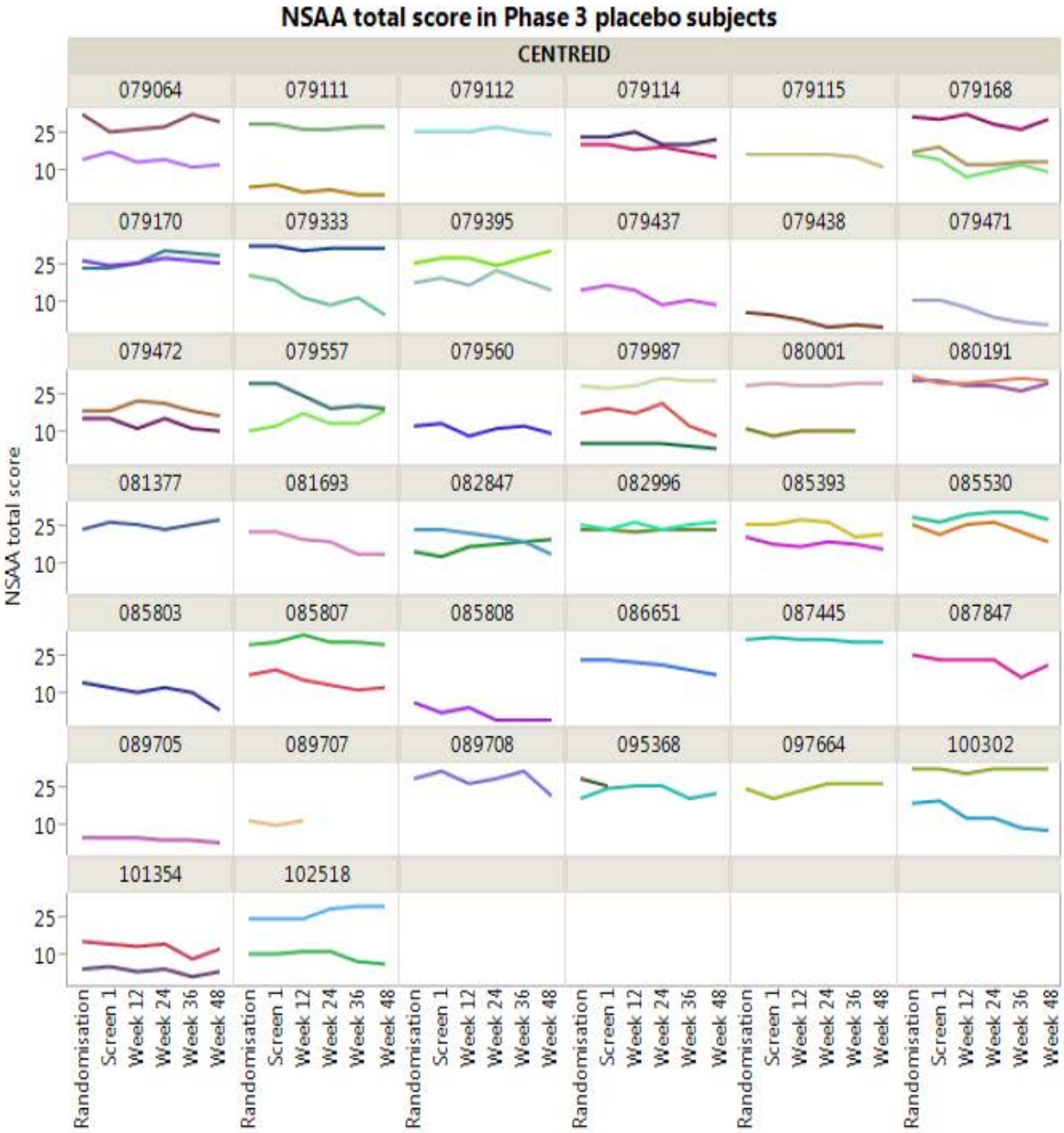
Screen 1
Screen 2
Week 1 Day 1
Week 12
Week 13
Week 24
Week 25
Week 37
Week 49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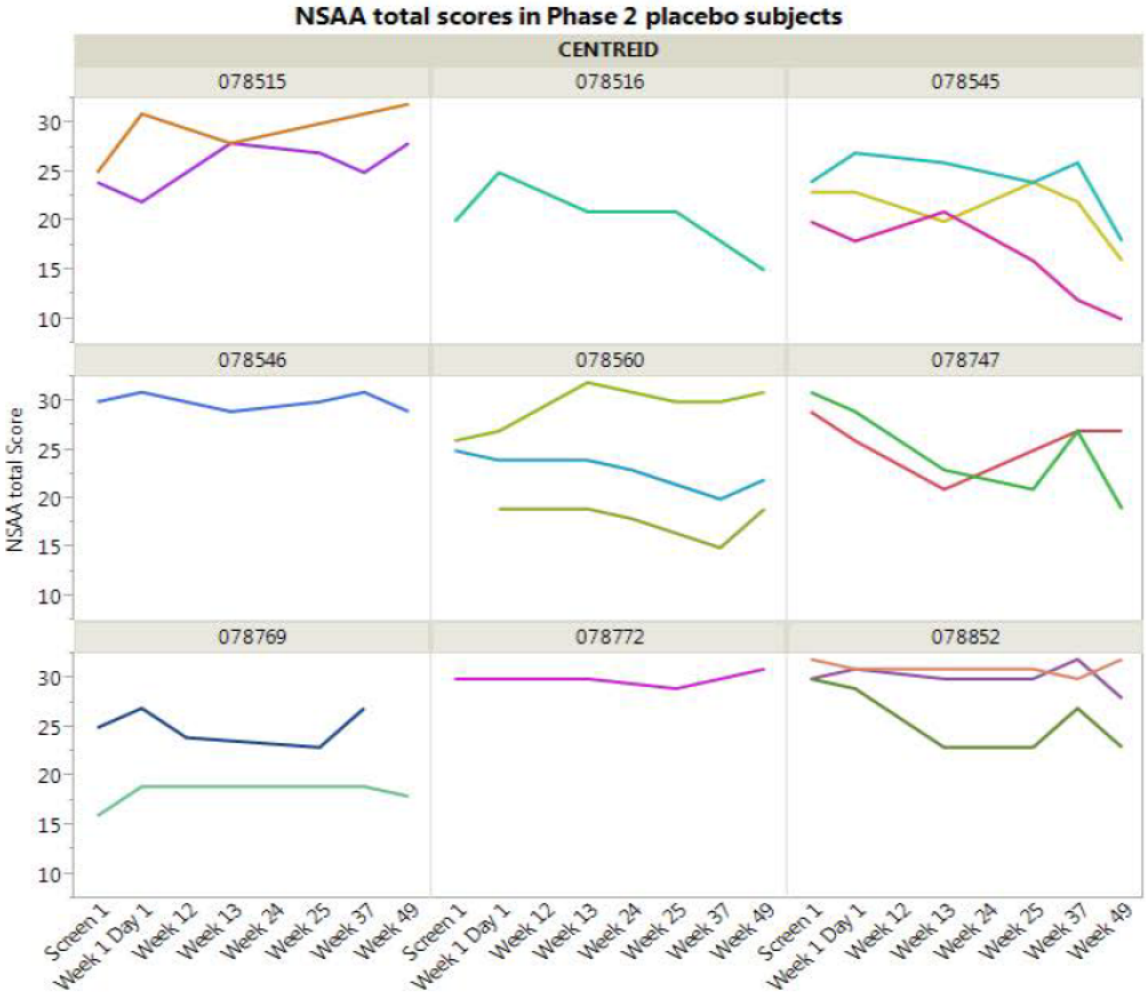
Week 36
Week 48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Week 1 Day 1
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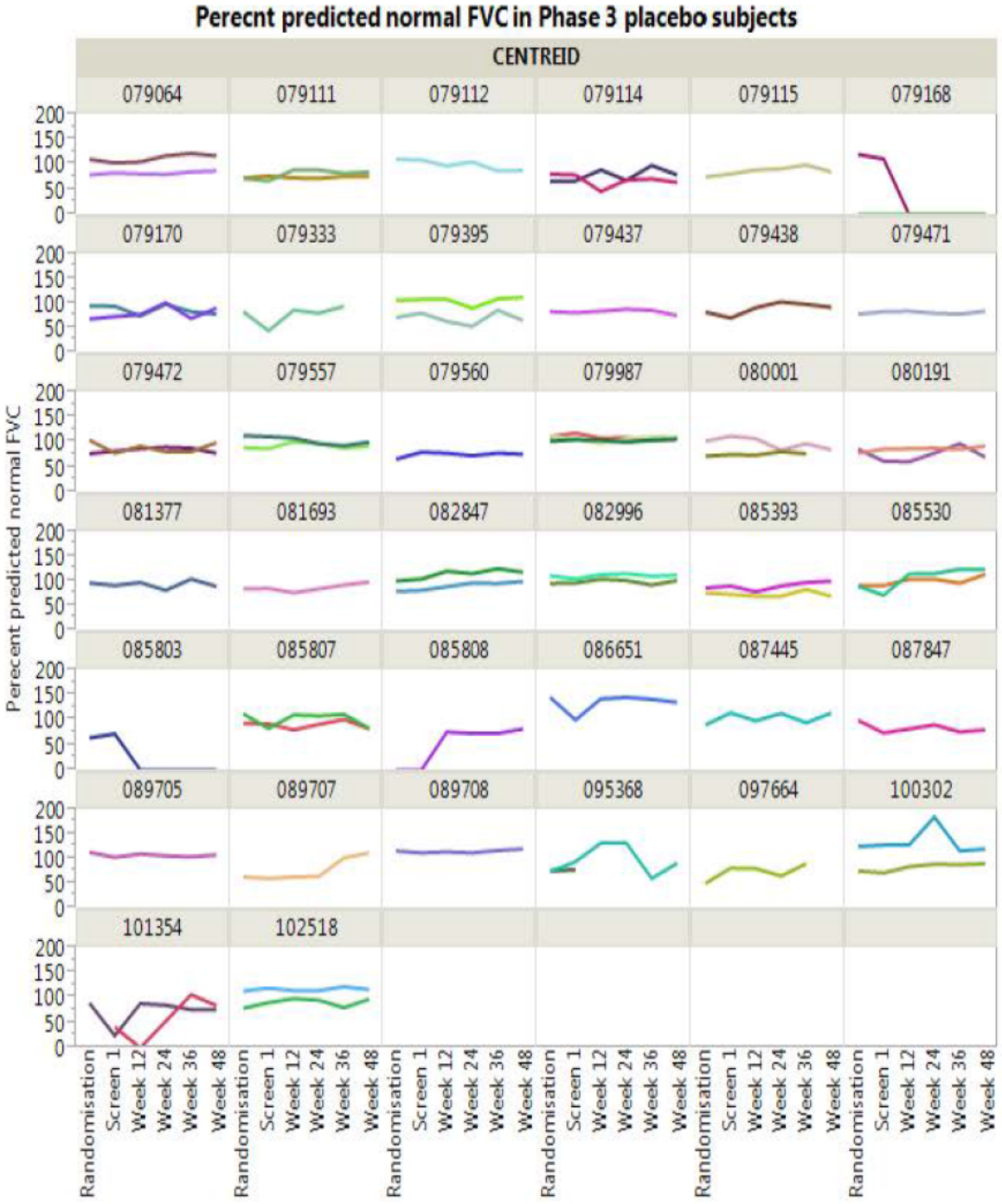
Week 13
Week 24
Week 25
Week 37
Week 49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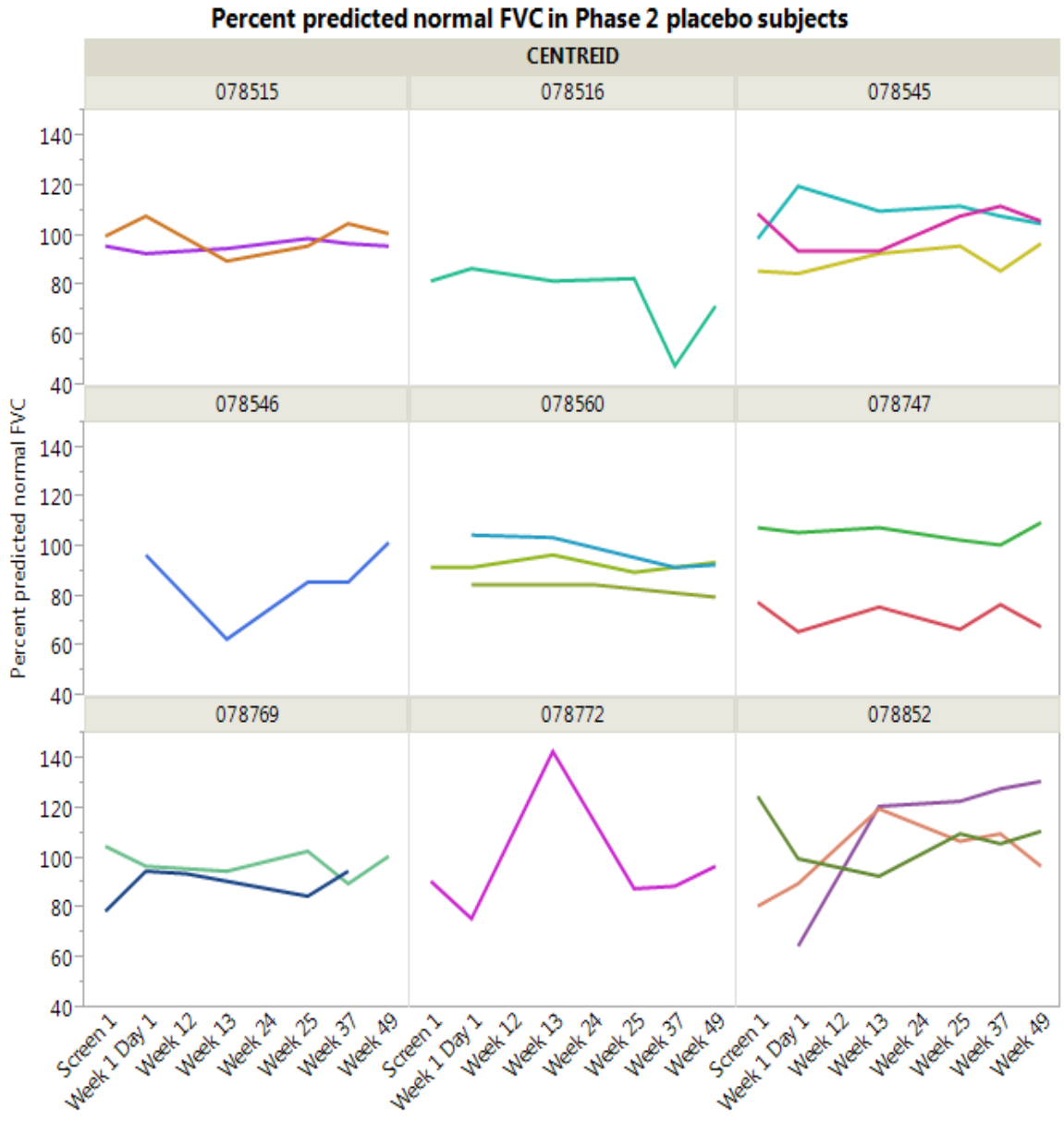
Week 48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Percent predicted normal FVC
140
120
100
80
60
40
Screen 1
Week 1 Day 1
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Week 25
Week 37
Week 49

IV. Clinical Safety Review

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	206031
Priority or Standard	Priority
Submit Date(s)	April 27, 2015
Received Date(s)	April 27, 2015
PDUFA Goal Date	December 27, 2015
Division/Office	Division of Neurology Products / Office of New Drugs
Reviewer Name(s)	Evelyn Mentari, M.D., M.S.
Review Completion Date	September 29, 2015
Established Name	Drisapersen
(Proposed) Trade Name	Kyndrisa
Applicant	BioMarin
Formulation(s)	Subcutaneous
Dosing Regimen	Loading dose: Initiate with 6 mg/kg twice weekly for the first 3 weeks of treatment Maintenance dose: 6 mg/kg once weekly (2.1)
Proposed Indication(s)	Duchenne muscular dystrophy (DMD) with mutations in the dystrophin gene that are amenable to treatment with exon 51 skipping as determined by genetic testing
Intended Population(s)	Patients with DMD (children and adults)
Recommendation on Regulatory Action	If the benefits outweigh the risks, then we recommend approval with labeling language including a boxed warning and a medication guide to mitigate the risks.

CDER Clinical Review Template Version date: April 9, 2015

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Glossary

AE	adverse event
aPTT	activated partial thromboplastin time
bpm	beats per minute
CHOP	Children's Hospital of Philadelphia
CIP	chronic intestinal pseudo-obstruction
CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
DIC	disseminated intravascular coagulation
DMD	Duchenne muscular dystrophy
ECG	electrocardiogram
FDA	Food and Drug Administration
GSK	GlaxoSmithKline
hERG	human ether-a-go-go-related gene
hsCRP	high sensitivity C-reactive protein
IDIC	independent data monitoring committee
INR	international normalized ratio
IND	investigational new drug application
ISS	integrated Summary of Safety
IU	International units
L	liter
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MCP-1	monocyte chemoattractant protein-1
msec	milliseconds
NDA	new drug application
OSI	Office of Scientific Investigations
OSE	Office of Surveillance and Epidemiology
PT	MedDRA Preferred Term
QTcB	QT interval value corrected according to Bazett's formula
QTcF	QT interval value corrected according to Friedericia's formula
REMS	risk evaluation and mitigation strategy
SAE	serious Adverse Event
SCS	Summary of Clinical Safety
SOC	MedDRA System Organ Class
ULN	Upper limit of normal

1 Executive Summary

1.1. Product Introduction

Drisapersen is a 2'-O-methyl-phosphorothioate oligonucleotide designed to skip exon 51 in dystrophin pre-mRNA to restore the reading frame of the mRNA. The proposed proprietary name is Kyndrisa. The proposed indication is the treatment of Duchenne muscular dystrophy (DMD) with mutations in the dystrophin gene that are amenable to treatment with exon 51 skipping as determined by genetic testing. Drisapersen is a new molecular entity.

The Sponsor's proposed loading dose is 6 mg/kg twice weekly for 3 weeks with a maintenance dose of 6 mg/kg once weekly. The route of administration is subcutaneous injection.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The reader is referred to the review of clinical efficacy by Dr. Veneeta Tandon.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Drisapersen is proposed to be used for treatment of Duchenne muscular dystrophy (DMD) in patients 5 years and older with mutations in the dystrophin gene that are amenable to treatment with exon 51 skipping as determined by genetic testing. This review evaluates the safety of drisapersen. If efficacy is demonstrated and the benefits of drisapersen outweigh the risks, then we recommend approval with labeling language including a boxed warning and a medication guide to mitigate the risks.

This document reviews the risk profile of drisapersen. Please refer to Dr. Veneeta Tandon's review for discussion of Analysis of Condition and Current Treatment Options and Benefit.

Risk:

Drisapersen is associated with severe and potentially life-threatening adverse effects. Drisapersen causes immune thrombocytopenia, renal toxicity, and skin injury at injection sites.

- Six drisapersen subjects (2%) had thrombocytopenia <20 x 10^9/L, levels at which patients are at risk potentially fatal complications, including spontaneous intracranial or intrapulmonary hemorrhage. Most of these patients had confirmed anti-platelet antibodies. These cases occurred 14-26 months after the first dose of drisapersen, suggesting that risk increases with duration of exposure. Platelet monitoring every 2 weeks, patient education regarding the signs and symptoms of thrombocytopenia, and facilitating prompt medical assessment and treatment can mitigate this risk. However, the decrease in platelets occurred precipitously and unpredictably, so that even with intensive monitoring, the risk remains. Concomitant use of antiplatelet, thrombolytic, or anticoagulant drugs is not recommended.
- Renal toxicity was reported in 61% of drisapersen 6 mg/kg/week subjects, compared to 34% of placebo subjects. Proteinuria was the most common renal toxicity and occurred in 44% of drisapersen 6 mg/kg/week subjects, compared to 23% of placebo subjects. One patient developed life-threatening thromboses with bilateral pulmonary emboli in the setting of glomerulonephritis with nephrotic syndrome. Renal laboratory monitoring every 2 weeks and cessation of drisapersen according to recommended laboratory criteria can mitigate this risk but will not eliminate the risk of severe and potentially fatal renal toxicity.
- Injection site reactions occurred in 79% of drisapersen patients and included ulceration, irreversible scarring, and atrophy. The risk for first injection site reaction occurred throughout the first 72 weeks of exposure. 21% of reactions were not resolved by the end of the studies. Reactions known to resolve lasted for a mean of 58 days and up to 1217 days.

Injection site reactions occurred despite administration by a medical professional and rotation of injection sites. No other strategies to mitigate the risk of injection site reactions are known.

- Drisapersen also has pro-inflammatory effects. It is not known how these effects or any other mechanism may have contributed to serious adverse events of myocarditis, myocardial ischemia, convulsion, intracranial venous sinus thrombosis, and small intestinal obstruction. The utility of monitoring inflammatory markers has not been evaluated.
- Phosphorothioate oligonucleotides are known to accumulate in the liver, and hepatic adverse events occurred in 10.5% subjects treated with drisapersen 6 mg/kg/week. Monitoring of liver function tests, including GGT, bilirubin, and INR, monthly will mitigate the risk of hepatic toxicity.

Paragraph #5

I recommend a patient registry as a post-marketing requirement to evaluate the main safety risks of drisapersen in the post-marketing setting. I recommend a boxed warning with recommendations for monitoring and administration to mitigate the risks of renal adverse events, thrombocytopenia, and injection site reactions and I recommend a Medication Guide to education patients about these risks.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Please refer to Dr. Tandon's review of clinical efficacy.	
Current Treatment Options	• Please refer to Dr. Tandon's review of clinical efficacy.	
Benefit	• Please refer to Dr. Tandon's review of clinical efficacy.	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk	• The safety database for drisapersen includes all patients from the 3 Phase 2 and Phase 3 placebo controlled trials and from the 3 open label studies. Drug exposure is adequate and reflects the intended population for use. • The most common AEs were: Proteinuria (60%); Injection site erythema (52%); Injection site discoloration (49%). • Six drisapersen subjects (2%) had thrombocytopenia <20 x 10^9/L, levels at which patients are at risk potentially fatal complications, including spontaneous intracranial or intrapulmonary hemorrhage. These cases occurred 14-26 months after the first dose of drisapersen. Despite routine monitoring of platelets every 2 weeks, thrombocytopenia occurred precipitously in some cases. • Renal toxicity occurred in 61% of patients taking drisapersen, and the risk for a renal adverse event existed throughout 72 weeks of exposure. Proteinuria occurred in 44% of drisapersen 6 mg/kg/week patients, compared to 23% of placebo patients. Proteinuria was generally reversible on discontinuation, although one patient had life-threatening glomerulonephritis with nephrotic syndrome and renal vein and inferior vena cava thrombi with bilateral pulmonary emboli. • Injection site reactions, including discoloration, induration, pain, pruritus, bruising, atrophy, hematoma, and swelling, occurred in 79% of drisapersen patients. Chronic skin damage and ulceration occurred in 18% and 7% drisapersen subjects, respectively. The risk for first injection site reaction occurred throughout the first 72 weeks of	Major safety issues of thrombocytopenia, renal toxicity, and injection site reactions, occur at the proposed dose of drisapersen. Hepatic accumulation is a class effect and hepatic adverse events occurred in the clinical trials. The safety issues can have life-threatening outcomes; the adverse reactions can be mitigated but not completely prevented with monitoring. The magnitude of the potential for serious harm after approval is unknown. Adherence to monitoring of platelets and renal laboratory parameters every two weeks is necessary, and failure to adequately monitor, recognize signs and symptoms, and provide prompt medical treatment in the postmarketing setting would increase the risk of adverse and potentially life-threatening outcomes. Injection site reactions occurred despite administration by a medical professional and rotation of injection sites. No other strategies to mitigate the risk of injection site reactions are known. Based on adverse events in nonclinical studies and because of limitations due to

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	exposure. 21% of reactions were not resolved by the end of the studies. Reactions known to resolve lasted for a mean of 58 days and up to 1217 days. • Phosphorothioate oligonucleotides are known to accumulate in the liver, and hepatic adverse events occurred in 10.5% subjects treated with drisapersen 6 mg/kg/week. The most common hepatic adverse event was increased glutamate dehydrogenase, which occurred in 5% of drisapersen 6 mg/kg/week patients in repeat dose studies and 2.5% for drisapersen 6 mg/kg/week in placebo-controlled studies, compared to 0% for placebo. • Concomitant use with antiplatelet, thrombolytic, or anticoagulant drugs is not recommended. Patients taking these drugs were excluded from clinical studies. • Safety in the postmarketing setting: Laboratory values as markers of renal, hepatic, and thrombocytopenia adverse events were closely monitored during the clinical studies, and close monitoring will be necessary in the postmarket setting if the drug is approved. • Other uncertainties: The clinical effects of anti-drisapersen antibodies are not known. The clinical effects of pro-inflammatory activity and whether these effects could have contributed to serious adverse events of myocarditis, myocardial ischemia, convulsion, intracranial venous sinus thrombosis, and small intestinal obstruction are not known. The utility of monitoring inflammatory markers has not been evaluated.	the small number of patients exposed and duration of exposure in the clinical trials, and the uncertainty related to clinical impact of pro-inflammatory effects, it is likely that adverse reactions not identified to date will occur in the postmarketing setting.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	• A patient registry as a post-marketing requirement will help to evaluate the main safety risks of drisapersen in the postmarketing setting. • Strong product labeling including a boxed warning and a Medication Guide with recommendations for monitoring of laboratory parameters and for rotation of injection sites is necessary to mitigate the risks of renal and thrombocytopenia adverse events and of injection site reactions. However, even with adequate monitoring, some patients will likely experience serious adverse events.	A patient registry as a post-marketing requirement will help to evaluate the main safety risks of drisapersen in the post-marketing setting. A boxed warning should be included in labeling to describe the risks of renal adverse events and thrombocytopenia and to provide recommendations for monitoring and to warning of the risk for injection site reactions and provide recommendations for rotation of injection sites. A medication guide should be required to describe these risks and symptoms of concern, and to highlight the need for prompt medical attention.

2 Therapeutic Context

2.1. Analysis of Condition

DMD is a severe, progressive, fatal pediatric neuromuscular disorder for which there is no available therapy. The disorder is caused by the absence of dystrophin protein due to mutations of the dystrophin gene. Dystrophin has a structural role as a cytoskeletal stabilization protein and protects muscle fibers against contraction-induced damage.[1] The disease occurs almost exclusively in males (X-linked recessive disorder) with an incidence of 1 in 3500 male births worldwide. Exon 51-skipping amenable mutations occur in approximately 13% of boys with DMD.

2.2. Analysis of Current Treatment Options

There are no FDA approved treatments for DMD. Corticosteroids are the standard of care.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Drisapersen is a new molecular entity, and it is not currently marketed in the U.S.

3.2. Summary of Presubmission/Submission Regulatory Activity

Summary of changes of sponsorship:

- Pre-IND sponsorship transferred from Prosensa to GlaxoSmithKline (GSK) on 10/6/2009
- IND sponsorship transferred from GSK back to Prosensa on 2/18/14
- BioMarin acquired Prosensa, including all subsidiaries, on 1/16/2015

Summary of designations:

- 8/25/09: Orphan designation granted
- 12/6/10: Fast Track designation granted
- 6/27/13: Breakthrough Therapy designation granted

[1] Rybakova,IN, et al. "The dystrophin complex forms a mechanically strong link between the sarcolemma and costameric actin." The Journal of cell biology 150.5 (2000): 1209-1214.

Regarding drug safety in humans, at a pre-IND meeting on July 8, 2009, the Agency expressed concern regarding hematological reactions and their reversibility. The Agency also provided input on the proposed renal and hepatic monitoring. Also in 2009, the Netherlands Medicine Evaluation Board and the sponsor agreed that thrombocytopenia is a class effect deemed important for monitoring in clinical studies.

On June 6, 2010, the IND was placed on Partial Clinical Hold, because of inadequate plans for safety monitoring. Increased laboratory monitoring, as well as study exclusion criteria based on platelet counts, coagulation and disseminated intravascular coagulation (DIC) laboratory tests, were added to clinical studies. The partial clinical hold was removed on May 4, 2011.

At an End-of Phase II meeting on May 23, 2013, the Agency agreed that the safety database was appropriate for NDA filing. At the pre-NDA meeting on January 27, 2015, the Agency indicated the additional analyses that were to be part of the NDA.

3.3. Foreign Regulatory Actions and Marketing History

There is no foreign marketing experience. A Marketing Authorization Application has been submitted to the European Medicines Agency with an opinion expected in 2016.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The reader is referred to the OSI review.

4.2. Product Quality

The reader is referred to the Office of Product Quality review.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

The reader is referred to the pharmacology/toxicology review.

4.5. Clinical Pharmacology

All clinical studies have been performed in subjects suffering from Duchenne muscular dystrophy (DMD), none in healthy volunteers. In theory, administration of drisapersen to healthy volunteers, and thereby skipping exon 51 of the DMD gene, could potentially alter a functional dystrophin protein into a non-functional form and was therefore considered unethical by the Sponsor. Production of a non-functional protein could induce side effects that would not be applicable to the subject population, where administration of the drug induces an in-frame transcript and a functional protein.

A human mass balance study using radiolabeled drisapersen (to determine mass balance, routes of excretion, identify and quantitate metabolites, etc.) has not been conducted. No human excretion data, including human urine measurements, have been evaluated with drisapersen.[2]

For additional information, the reader is referred to the clinical pharmacology review.

4.5.1. Mechanism of Action

Drisapersen is a 2'-O-methyl-phosphorothioate oligonucleotide designed to skip exon 51 in dystrophin pre-mRNA to restore the reading frame of the mRNA. Restoring the reading frame of the dystrophin gene may result in the expression of a truncated but functional dystrophin protein.

4.5.2. Pharmacodynamics

The reader is referred to the review of clinical efficacy for analyses of muscle biopsy and biomarker results.

4.5.3. Pharmacokinetics

The plasma concentrations of drisapersen increased rapidly after drug administration and, for the majority of subjects, reached maximum plasma concentrations 2 and 3 hours post-dose. Thereafter, drisapersen was rapidly distributed to tissues with a decline in plasma levels to about 18% of the Cmax at 24 hours post-dose and to about 0.6% of Cmax at the end of the dosing interval.

In Study DMD114673, muscle concentrations of drisapersen determined in muscle biopsies obtained after 5 weeks (Visit 8), 6 months (Visit 37) and after 1.5 years (Visit 81) of subcutaneous administrations of 6 mg/kg were detected in all samples analysed (see Table 15). A variance between individual subjects is found, ranging from 3.3 to 9.9 µg/g after 5 weeks, from 5.8 to 28.4 µg/g after 6 months and from 8.7 to 39.1 µg/g after 1.5 years. Overall, muscle tissue concentrations of drisapersen increased between 5 weeks and 6 months of drisapersen

[2] P. 50-51 Summary of Clinical Pharmacology. Submitted to NDA206031 on 4/27/2015.

treatment, and for four subjects between 6 months and 1.5 years of drisapersen treatment.

In study DMD114876, drisapersen treatment duration was 24 weeks; beyond this time frame drisapersen levels were maintained and decreased only slowly. The mean level of drisapersen in tissue homogenates at Week 36, 12 weeks after stopping treatment, had declined by 41%. Both the slow accumulation and the slow elimination from tibialis anterior muscle tissue suggest a tissue half-life for drisapersen in muscle in the range of 2-3 months.

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

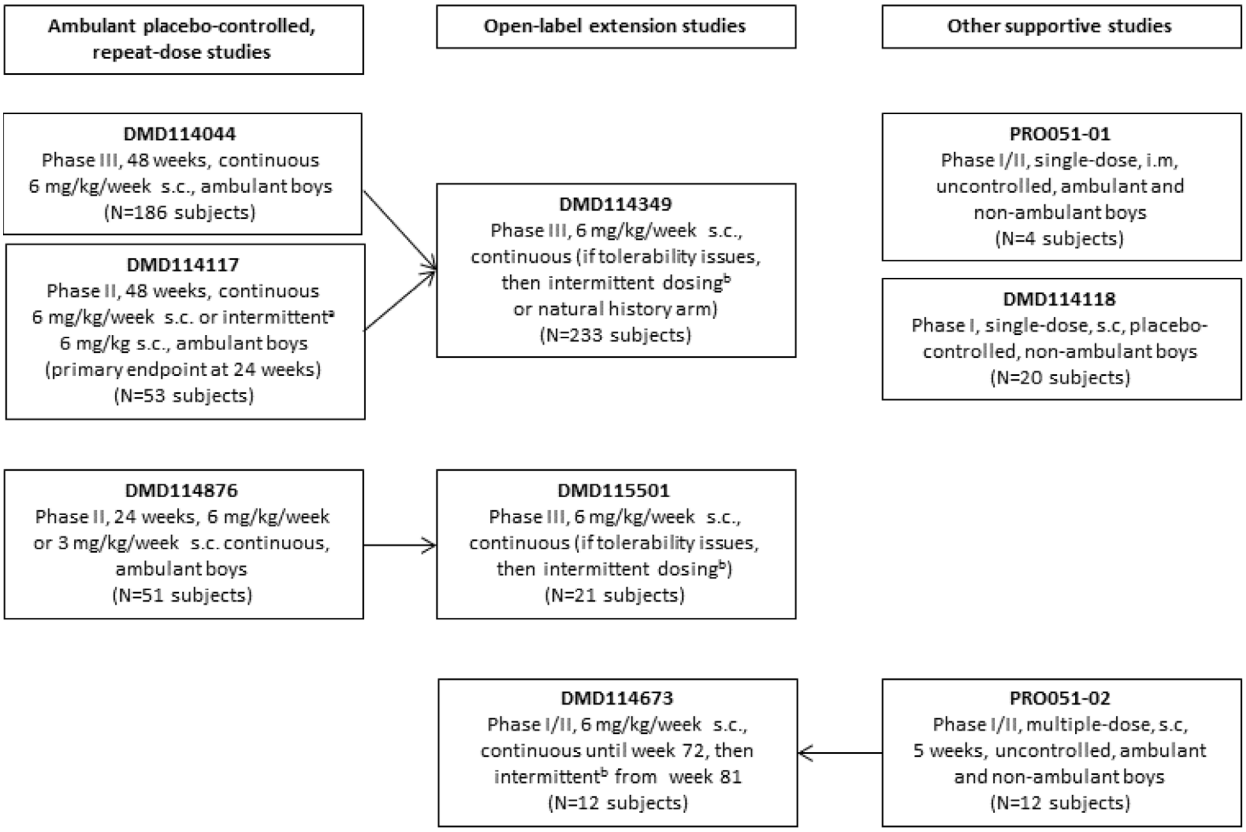
Not applicable.

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The figure below provides an overview of the drisapersen clinical development program. The table below summarizes clinical studies supporting safety in NDA 206031.

Figure 1. Overview of the drisapersen clinical program



Source: Sponsor Figure 2. P. 16 Summary of Clinical Safety. Submitted to NDA 206031 on 4/27/2015.
a Intermittent dosing in DMD114117 - alternating 6mg/kg/week twice weekly and 6 mg/kg/week for 6 weeks followed by 4 week off-dose period
b Intermittent dosing in DMD114349, DMD114673,and DMD115501- 6 mg/kg/week for 8 weeks followed by 4 weeks off-dose

Table 1. Listing of clinical studies to support safety in NDA 206031

Trial Identity	Trial Design	Regimen/ schedule/ route	Treatment Duration	No. of Subjects	Study Population	Countries
Placebo-controlled studies						
DMD114044	Randomized, double-blind, placebo-controlled	Drisapersen, solution for injection, s.c.6 mg/kg/week Dose-matched placebo	48 weeks	Total: 186 6mg/kg/week: 125 Placebo: 61	Ambulant boys with DMD	Argentina, Belgium, Brazil, Canada, Chile, Czech Republic, Denmark, France, Germany, Italy, Japan, Republic of Korea, Netherlands, Norway, Poland, Russian Federation, Spain, Taiwan, Turkey
DMD114117	Randomized, double-blind, placebo-controlled	Drisapersen, solution for injection, s.c. 6 mg/kg twice weekly for 3 weeks (loading dose) then either: Continuous: 6 mg/kg/week or Intermittent: 6 mg/kg twice weekly on 1st, 3rd and 5th weeks, once weekly on 2nd, 4th and	48 weeks	Total: 53 6 mg/kg/week:18 Intermittent 6 mg/kg: 17 Placebo: 18	Ambulant boys with DMD	Australia, Belgium, France, Germany, Israel, Netherlands, Spain, Turkey, UK

Trial Identity	Trial Design	Regimen/ schedule/ route	Treatment Duration	No. of Subjects	Study Population	Countries
		6th weeks, and no active drug on 7th to 10th week of each 10 week cycle. Placebo, dose–matched placebo twice weekly for 3 weeks (loading dose) then weekly				
DMD114876	Randomized, double-blind, placebo-controlled	Drisapersen 3 mg/kg, drisapersen 6 mg/kg, given s.c. once a week. Dose-matched placebo for both active arms	24 weeks	Total: 51 3mg/kg/week: 17 6mg/kg/week: 18 Placebo: 16	Ambulant boys with DMD	USA
Other repeat dose study						
PRO051-02	Randomized open label	Drisapersen, solution for injection, s.c. 0.5 mg/kg/week 2.0 mg/kg/week 4.0 mg/kg/week 6.0 mg/kg/week	5 weeks	Total: 12 3 subjects in each treatment arm	Ambulant and non-ambulant boys with DMD	Belgium, Sweden
Open-label extension studies						
DMD114349 (extension study to DMD114117 & DMD114044)	Open label	Drisapersen, solution for injection, s.c.6 mg/kg/week Subjects who met laboratory or follow-up stopping criteria or with tolerability issues had option to enter intermittent arm of 6 mg/kg/week for 8 weeks followed by 4 weeks off dose.	Minimum 104 weeks of treatment	233	Boys with DMD ambulant at the start of the parent study	Argentina, Australia, Belgium, Brazil, Bulgaria, Canada, Chile, Czech Republic, Denmark, France, Germany,

Trial Identity	Trial Design	Regimen/ schedule/ route	Treatment Duration	No. of Subjects	Study Population	Countries
		Subjects who did not wish to receive drisapersen or who had to withdraw from both active arms during the study had the option to go into a natural history observation arm				Hungary, Israel, Italy, Japan, Republic of Korea, Netherlands, Norway, Poland, Russian Federation, Spain, Taiwan, Turkey, UK.
DMD114673 (extension to PRO051-02)	Open label	Drisapersen solution for Injection 6 mg/kg s.c. for 72 weeks. After an interval off drug of 8 weeks (Weeks 73 – 80), all subjects restarted an intermittent treatment regimen of 6 mg/kg/week for 8 weeks, followed by 4 weeks off treatment = 12 weeks per cycle up to 188 weeks.	188 weeks s.c. in all 12 subjects. Subjects then received iv (5 doses), s.c. or iv (5 doses) and s.c. for a further 27 weeks until dosing was halted.	12	Subjects with DMD, ambulant and non-ambulant boys who completed the initial study	Belgium, Sweden
DMD115501 (extension to DMD114876)	Open label	Drisapersen, solution for injection, s.c.6 mg/kg/week Subjects who met laboratory or follow-up stopping criteria or with	Treatment until withdrawal criteria met or	Study in progress at the time of NDA submission. Aims to enroll about 72 subjects	Boys with DMD ambulant at the start of the	USA

Trial Identity	Trial Design	Regimen/ schedule/ route	Treatment Duration	No. of Subjects	Study Population	Countries
		tolerability issues had option to enter intermittent arm of 6 mg/kg/week for 8 weeks followed by 4 weeks off dose.	sponsor stops the study.		parent study	

Abbreviations: DMD=Duchenne Muscular Dystrophy; iv=intravenous; s.c.=subcutaneous.

5.2. Review Strategy

The clinical review of NDA 206031 is divided into a review of clinical efficacy (by Dr. Veneeta Tandon) and this review of clinical safety.

Information submitted as part of NDA 206031, as well as published information related to the oligonucleotides as a pharmacologic class and other relevant published literature, are discussed in this review.

6 Review of Relevant Individual Trials Used to Support Efficacy

Not applicable to the review of clinical safety. The reader is referred to the review of clinical efficacy by Dr. Veneeta Tandon.

7 Integrated Review of Effectiveness

Not applicable to the review of clinical safety. The reader is referred to the review of clinical efficacy by Dr. Veneeta Tandon.

8 Review of Safety

Safety Review Approach

Two main safety subject pools were used in the analyses of drisapersen clinical safety.

1. Placebo-controlled studies:

- DMD114044 (Phase 3)
- DMD114117 (Phase 2)
- DMD114876 (Phase 2)

2. Repeat dose studies (6 studies in total), which includes the 3 placebo-controlled studies, as well as 3 open label studies:

- PRO051-02
- DMD114349 (Extension study of DMD114044 and DMD114117)
- DMD114673 (Extension study of PRO051-02)

For additional details on these studies, the reader is referred to Section 5.1.

Safety issues of interest identified during drug development included:

- Thrombocytopenia
- Renal toxicity
- Injection site reactions
- Inflammation
- Coagulation disorders
- Hepatic disorders

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The tables below describe the size and subject duration of exposure for the drisapersen safety population.

Table 2. Drisapersen Safety Population. Size and Denominators

Drisapersen Safety Database for treatment of Duchenne Muscular Dystrophy (DMD) (N=312)			
Clinical Trial Groups	Drisapersen (n= 312)	Active Control (n=0)	Placebo (n= 95)
Normal Volunteers	0	0	0
Controlled trials conducted for DMD indication	195	0	95
All other than controlled trials conducted for DMD indication	117	0	0
Controlled trials conducted for other indications	0	0	0

Source: Sponsor Tables 12 and 13. Summary of Clinical Safety.

Table 3. Drisapersen Safety Population. Duration of Exposure

Number of patients exposed to the study drug:			
≥24 weeks	≥48 weeks	≥72 weeks	≥96
N= 271	N= 223	N=192	N=122

Source: Sponsor Table 15. Summary of Clinical Safety.

When compared to International Conference on Harmonisation (ICH) guidelines,[3] the overall number of exposed subjects is less than the usual recommendation. However, because DMD is a rare disease, there is no specific minimum number of patients that should be studied to establish clinical safety. The number of subjects exposed ≥6 months nearly meets the ICH recommendation, and the number of subjects exposed ≥ 1 year exceeds the recommendation.

8.2.2. Relevant characteristics of the safety population:

Demographics

The table below displays demographics for subjects in all repeat-dose studies. The median age in drisapersen 6 mg/kg/week subjects was 8 years, compared to 7 years in placebo subjects. There were a total of 51 subjects from the United States.[4]

[3] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures must occur at the dose or dose range believed to be efficacious. (ICH E-1)
[4] Data from dataset ADSL2. Submitted to NDA 206031 on June 5, 2015.

Table 4. Summary of demographic characteristics (repeat dose studies)

	Placebo N=95	Drisapersen 3mg/kg/wk N=17	Drisapersen 6mg/kg/wk N=267	Drisapersen 6mg/kg intermittent [a] N=17	Drisapersen 6mg/kg intermittent [a] N=24	Drisapersen all regimens [c] N=285
Age[d] group, n (%)						
≤7 years	48 (50.5)	8 (47.1)	123 (46.1)	7 (41.2)	5 (20.8)	132 (46.3)
>7 years	47 (49.5)	9 (52.9)	144 (53.9)	10 (58.8)	19 (79.2)	153 (53.7)
Age[d], years						
Mean (SD)	7.8 (2.13)	7.8 (1.91)	8.3 (2.25)	7.7 (1.49)	9.3 (2.07)	8.3 (2.22)
Median	7.0	8.0	8.0	8.0	9.0	8.0
Min, max	5, 16	5, 11	5, 16	5, 10	5, 14	5, 16
Ethnicity, n (%)						
Hispanic/Latino	14 (14.7)	1 (5.9)	34 (12.7)	1 (5.9)	2 (8.3)	35 (12.3)
Non-Hispanic/Latino	79 (83.2)	16 (94.1)	216 (80.9)	14 (82.4)	10 (41.7)	233 (81.8)
Missing	2 (2.1)	0	17 (6.4)	2 (11.8)	12 (50.0)	17 (6.0)
Race, n (%)						
African American/African	2 (2.1)	1 (5.9)	2 (0.7)	0	0	3 (1.1)
American Indian/Alaskan native	0	0	1 (0.4)	1 (5.9)	0	1 (0.4)
Asian – central//South	1 (1.1)	0	4 (1.5)	0	0	4 (1.4)
Asian - East	3 (3.2)	0	10 (3.7)	0	0	10 (3.5)
Asian - Japanese	5 (5.3)	0	14 (5.2)	0	1 (4.2)	14 (4.9)
Asian - South-East	1 (1.1)	0	4 (1.5)	0	1 (4.2)	4 (1.4)
Native Hawaiian, other Pacific islander	1 (1.1)	0	1 (0.4)	0	0	1 (0.4)
White – arabic/North African	4 (4.2)	0	11 (4.1)	0	1 (4.2)	11 (3.9)
White – Caucasian/European	73 (76.8)	16 (94.1)	208 (77.9)	14 (82.4)	20 (83.3)	225 (78.9)
Mixed race	3 (3.2)	0	7 (2.6)	0	1 (4.2)	7 (2.5)
Missing	2 (2.1)	0	5 (1.9)	2 (11.8)	0	5 (1.8)
Region, n (%)						
Europe	47 (49.5)	0	149 (55.8)	12 (70.6)	19 (79.2)	149 (52.3)
North America	23 (24.2)	17 (100)	38 (14.2)	0	1 (4.2)	55 (19.3)
Asia	7 (7.4)	0	23 (8.6)	0	1 (4.2)	23 (8.1)
Rest of World	18 (18.9)	0	57 (21.3)	5 (29.4)	3 (12.5)	58 (20.4)

Source: Sponsor Table 23. Summary of Clinical Safety p. 56.
Table includes data from studies DMD114117, DMD114044, DMD114876, DMD114349, PRO051-02, and DMD114673.

Inclusion and Exclusion Criteria

The study inclusion and exclusion criteria are summarized in Summary of Clinical Safety Appendix 8.1.

All studies [except for open label study PRO051-02 (N=12)] included only ambulant subjects. The clinical study findings may not fully represent drisapersen clinical safety in the setting of more advanced DMD. Also, the pharmacokinetics of drisapersen may be different in the non-ambulant population, because of differences in muscle mass.

Drisapersen clinical studies excluded patients with current or a history of liver or renal disease.

8.2.3. Adequacy of the safety database

Because DMD is a rare disease, the overall subject exposure in the drisapersen clinical development program is adequate. Duration of treatment and patient demographics are acceptable.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The NDA submission was well-organized. Requests for additional information were handled promptly by the Sponsor.

8.3.2. Categorization of Adverse Events

The Sponsor's process for recording AEs was appropriate. The Sponsor's coding resulted in appropriate translation of verbatim terms to preferred terms. However, AEs were often coded to multiple different equivalent Preferred Terms, which resulted in splitting of adverse events across multiple Preferred Term categories. For example, in placebo-controlled studies, proteinuria (including adverse events with PTs Proteinuria, Protein urine present, and Protein urine) occurred in 44% drisapersen 6 mg/kg/week subjects, compared to the table listing of 29%, which only included adverse events coded to the PT Proteinuria.

The Sponsor categorized adverse events as mild, moderate, or severe. Adverse events were coded to MedDRA 16.1 in the integrated summary of safety.

Adverse events with onset after the first dose up to 28 days after the last dose were considered on-treatment AEs. Those occurring from day 29 after the last dose were considered follow-up AEs. Treatment-emergent AEs were composed of on-treatment and follow-up AEs.[5]

8.3.3. Routine Clinical Tests

The laboratory assessment schedule in the drisapersen clinical development program is summarized in Appendix Section 13.3.[6] Most laboratory measurements related to adverse events of special interest (e.g., renal monitoring and platelet counts) were performed every 2 weeks.

Reviewer comment: In the opinion of this reviewer, the safety assessment methods in drisapersen clinical studies were acceptable.

8.4. Safety Results

[5] P. 26 Summary of Clinical Safety.
[6] Summary of Clinical Safety section 8.3.

8.4.1. Deaths

No subjects died during the drisapersen clinical development program.

8.4.2. Serious Adverse Events

Serious adverse events (SAEs) from the Integrated Summary of Safety (ISS) pool[7] of all repeat dose studies are summarized in the table below. Forty six of 285 (16.1%) drisapersen subjects (all regimens) had at least 1 SAE.

Table 5. Summary of All Serious Adverse Events by System Organ Class, Ordered by Decreasing Frequency (Safety): Repeat-Dose studies

System Organ Class:	Placebo (n=95) n (%)	Drisapersen 6mg/kg (n=267) n (%)	Drisapersen 6mg/kg Intermittent (n=38) n (%)	Drisapersen All Regimens (n=285) n (%)
Any SAE	9 (9.5)	44 (16.5)	4 (10.5)	46 (16.1)
Injury, Poisoning And Procedural Complications	3 (3.2)	12 (4.5)	1 (2.6)	12 (4.2)
Blood And Lymphatic System Disorders	0	9 (3.4)	0	9 (3.2)
Cardiac Disorders	0	4 (1.5)	1 (2.6)	5 (1.8)
Gastrointestinal Disorders	1 (1.1)	4 (1.5)	0	4 (1.4)
Musculoskeletal And Connective Tissue Disorders	0	4 (1.5)	0	4 (1.4)
Nervous System Disorders	1 (1.1)	4 (1.5)	0	4 (1.4)
Renal And Urinary Disorders	0	3 (1.1)	1 (2.6)	4 (1.4)
General Disorders And Administration Site Conditions	0	3 (1.1)	0	3 (1.1)
Infections And Infestations	4 (4.2)	3 (1.1)	0	3 (1.1)
Eye Disorders	0	2 (0.7)	0	2 (0.7)
Hepatobiliary Disorders	0	2 (0.7)	0	2 (0.7)
Investigations	0	2 (0.7)	0	2 (0.7)
Metabolism And Nutrition Disorders	0	2 (0.7)	0	2 (0.7)
Ear And Labyrinth Disorders	0	0	1 (2.6)	1 (0.4)
Reproductive System And Breast Disorders	0	1 (0.4)	0	1 (0.4)
Surgical And Medical Procedures	0	1 (0.4)	0	1 (0.4)

Source: Table 5. ISS addendum. Section 5.3.5.3 Sponsor Response submitted to NDA 206031 on 7/24/2015.
Subjects are counted once in each treatment group they were dosed in and once in the 'All regimens' group.

Reviewer comment: I reviewed subject narratives, as well as other documents as necessary, in the assessment of the clinical study SAEs. There were no adverse events of aplastic anemia,

[7] Study 115501 (extension study to DMD114876) (N=21) was not included in the ISS pool of all repeat dose studies, because it was ongoing at the NDA data cut-off date. Data from Study 115501 was subsequently requested and reviewed. There were two SAEs from this study (PTs Appendicitis and Femur fracture). The overall drisapersen safety profile in Study 115501 was similar to other studies in the drisapersen clinical development program. There were no additional Serious adverse events reported during the incremental 120-day safety update period. (P. 52 of the 120-Day Safety Update Report. Submitted to NDA 206031 on 8/24/2015.)

pancytopenia, acute pancreatitis, Stevens Johnson Syndrome, toxic epidermal necrolysis, or drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome reported in the drisapersen clinical development program.

Injury, Poisoning, and Procedural Complications SOC

Twelve of 285 (4.2%) subjects in repeat dose studies had SAEs coded to the Injury, Poisoning, and Procedural Complications SOC (see table below).

Table 6. Serious Adverse Events. Injury, Poisoning, and Procedural Complications SOC. Repeat dose studies. Integrated Summary of Safety analysis.

System Organ Class Preferred Term	Placebo (n = 95)	Drisapersen 6mg/kg (n = 267)	Drisapersen 6mg/kg Intermittent (n = 38)	Drisapersen All Regimens (n = 285)
Injury, Poisoning And Procedural Complications	3 (3.2%)	12 (4.5%)	1 (2.6%)	12 (4.2%)
Femur Fracture	0	6 (2.2%)	1 (2.6%)	7 (2.5%)
Tibia Fracture	0	3 (1.1%)	0	3 (1.1%)
Ankle Fracture	0	1 (0.4%)	0	1 (0.4%)
Fall	0	1 (0.4%)	0	1 (0.4%)
Head Injury	1 (1.1%)	1 (0.4%)	0	1 (0.4%)
Lumbar Vertebral Fracture	0	1 (0.4%)	0	1 (0.4%)
Wound Dehiscence	0	1 (0.4%)	0	1 (0.4%)
Avulsion Fracture	1 (1.1%)	0	0	0
Toxicity To Various Agents	1 (1.1%)	0	0	0

Source: Table 6. ISS addendum. Section 5.3.5.3 Sponsor Response submitted to NDA 206031 on 7/24/2015.

Fractures

In placebo-controlled studies, 12 of 195 (6.2%)[8] drisapersen subjects had a fracture AE, compared to 5 of 95 (5.3%) placebo subjects. In placebo-controlled studies, 4[9] of 195 (2.1%) drisapersen subjects had a fracture SAE, compared to 1[10] of 95 (1.1%) placebo subjects.

In extension studies, an additional 6 drisapersen subjects had a fracture SAE.[11]

[8] Drisapersen fracture count includes 11 cases listed in the table, as well 1 additional fracture described in an SAE narrative (DMD114044 Subject 678; PT Head injury).
Source: Table 11a. P. 4 ISS addendum. Submitted to NDA 206031 on August 20, 2015.
[9] DMD114044 Subjects 184 (femur fracture), 512 (femur fracture, 598 (tibia and lumbar vertebral fracture), and 678 [skull trauma with a linear skull fracture after a fall while playing (PT Head injury)]
[10] DMD114044 Subject 1367 (Avulsion fracture of the right patella)
[11] DMD114673 Subject 103 (femur fracture and tibia fracture); DMD114349 Subject 1302 (femur fracture); DMD114349 Subject 1305 (femur fracture); DMD114349 Subject 1307 (femur fracture); DMD114349 Subject 1367

Reviewer comment: In placebo-controlled studies, the incidence of fractures was similar in drisapersen and placebo groups. These SAEs are likely related to DMD. Fractures are a significant problem in the DMD population. In a retrospective study of 378 DMD patients (median age 12 years, range 1-25 years), 20.9% had experienced at least one fracture. [12] *There are a number of mechanisms involved, including reduced muscle tension on bone, chronic corticosteroid use, and altered calcium and Vitamin D homeostasis.*[13]

Other Injury, Poisoning, and Procedural Complications SOC SAEs

In repeat dose studies, there were 4 other SAEs in this SOC (2 in drisapersen subjects and 2 in placebo subjects):

- DMD114044 Subject 526 (drisapersen 6 mg/kg/week): accidental fall that ruptured recent muscle biopsy sutures (PT Fall) (*Unrelated to drisapersen)*
- DMD114044 Subject 638 (drisapersen 6 mg/kg/week): wound dehiscence of a muscle biopsy site (PT Wound dehiscence) (*Unrelated to drisapersen)*
- DMD114117 Subject 2078 (placebo): head injury while playing (PT Head injury)
- DMD114044 Subject 504 (placebo): drug toxicity from clonazepam (PT Toxicity to various agents)

Blood and lymphatic system disorders SOC

In placebo-controlled studies, there were no SAEs coded to the Blood and lymphatic system disorders SOC. Nine of 285 (3.2%) drisapersen-treated subjects in repeat-dose studies had SAEs in this SOC:

- Eight subjects had SAEs with the PT Thrombocytopenia;[14] Details of these SAEs are included in the evaluation of thrombocytopenia in Section 8.5.1

- DMD114349 subject 516, a 13 year old male from France, had SAEs coded to the PTs Haemolytic anemia and Hepatocellular injury in the setting of a mycoplasma infection.[15] On (b) (6), 957 days after the start of drisapersen treatment and 5 days after the most recent dose, he was hospitalized with asthenia, jaundice, and

(femur fracture and ankle fracture);and DMD114349 Subject 2202 (tibia fracture). Note: Subject 1367 also had an avulsion fracture while randomized to placebo in Study 114044.

[12] McDonald DGM, et al. "Fracture prevalence in Duchenne muscular Dystrophy." *Developmental Medicine & Child Neurology* 2002, 44: 695–698.

[13] Morgenroth VH, et al. "Insights into bone health in Duchenne muscular dystrophy." *BoneKEy Reports* 1, Article number: 9 (2012).

[14] DMD114349 subjects 505, 677, 687, 1122, 1176, 1202, 2000, and 3052.

[15] Narrative on ISS p. 3821; Section 5.3.5.3 of the April 27, 2015 submission to NDA 206031.

gastroenteritis for the preceding 48 hours, with abdominal pain, diarrhea, fever (38°C), mucosal pallor, and dark urine. Hemoglobin was 5.1 g/dL on hospital admission. Other laboratory assessments included ALT 367 U/L and AST 233 U/L. (In Study DMD114044 on August 11, 2011, the subject had an elevated GGT of 169 IU/L with ALT 800 IU/L and AST 453 IU/L; no adverse event was reported related to these laboratory measurements on 8/11/2011.) No GGT or bilirubin measurements from hospital admission were provided by the Sponsor. On (b) (6) GGT was 254 IU/L (normal range 0-65 IU/L). Mycoplasma pneumoniae IgM was positive, according to the hospital report of (b) (6) (no baseline value was available).[16] He was treated with josamycin. The event of hepatocellular injury was considered resolved on (b) (6), and the event of hemolytic anemia was considered resolved on (b) (6). Treatment with drisapersen was discontinued at the start of this SAE and was not resumed, because all dosing in the study was suspended at the time the events resolved.

Reviewer comment: This subject was Coombs test positive, and mycoplasma pneumonia IgM was positive. This is consistent with autoimmune hemolytic anemia related to mycoplasma infection.[17] Hepatic abnormalities can occur with mycoplasma infection. It is unclear whether hepatic toxicity related to drisapersen contributed to his hepatic abnormalities.

Cardiac Disorders SOC

Five of 285 (1.8%) subjects in repeat dose studies had SAEs coded to the Cardiac Disorders SOC (see table below).

Table 7. Serious Adverse Events. Cardiac Disorders SOC. Repeat dose studies. Integrated Summary of Safety analysis.

System Organ Class Preferred Term	Placebo (n = 95)	Drisapersen 6mg/kg (n = 267)	Drisapersen 6mg/kg Intermittent (n = 38)	Drisapersen All Regimens (n = 285)
Cardiac Disorders	0	4 (1.5%)	1 (2.6%)	5 (1.8%)
Cyanosis	0	2 (0.7%)	0	2 (0.7%)
Cardiac Fibrillation	0	1 (0.4%)	0	1 (0.4%)
Myocardial Ischaemia	0	1 (0.4%)	0	1 (0.4%)
Myocarditis	0	0	1 (2.6%)	1 (0.4%)

Source: Table 6. ISS addendum. Section 5.3.5.3 Sponsor Response submitted to NDA 206031 on 7/24/2015.

[16] P. 1373 Study 114349 subject 516 case report form. Submitted to NDA 206031 on 4/27/2015.
[17] *Mycoplasma pneumoniae* and Its Role as a Human Pathogen. Waites KB, et al. Clin. Microbiol. Rev. October 2004 vol. 17 no. 4 697-728.

In placebo-controlled studies, 3 of 195 (1.5%) drisapersen subjects had an SAE in the Cardiac Disorders SOC, compared to 0 of 95 placebo subjects:

- DMD114044 Subject 1111,[18] a 6 year old male from Chile with no previous cardiac medical history and no relevant concomitant medications, had an SAE coded to the PT Myocardial ischemia. He had acute precordial chest pain, and ECG was reported as consistent with subendocardial ischemia. Cardiac enzymes were not performed. Echocardiogram was normal. ECG changes and chest pain resolved on the same day after a period of observation. Drisapersen was withheld for 4 weeks.
  Reviewer comment: This SAE is possibly related to drisapersen. Myocardial ischemia is rare in children. No structural cardiac abnormalities were reported on echocardiogram. There is evidence of increased inflammation with drisapersen, and vascular inflammation is a possible drug-related cause for this SAE. He tested positive for anti-drisapersen antibodies.[19] Inflammatory markers at the time of the event (April 20-25, 2012) were not measured. On May 9, 2012 he had an elevated sensitivity C-reactive protein (hsCRP) level of 7.9 mg/L.[20] (It is unclear to what degree this laboratory value is drug related.) Prior to the SAE, this subject's hsCRP levels were 0.2-0.6 mg/L.

- DMD114117 Subject 2132, a 6 year old boy from Spain, had an SAE coded to the PT Myocarditis that occurred on December 2, 2011, approximately 2 months after starting drisapersen. Serology results for coxsackie virus from December 16, 2011 include: coxsackie virus IgG 395 U/mL (normal range: 80 – 100); and coxsackie virus IgM: 45 U/mL (normal range: 30 – 50).[21] No endomyocardial biopsy was performed. No action was taken with drisapersen in response to this myocarditis event. He had no pericarditis. The event was reported to be resolved with sequelae. (Sequelae were not reported.)[22]
  Reviewer comment: This subject had an SAE of myocarditis in the setting of a positive coxsackie virus serology. Myocarditis is a rare event in children. This event may be an event of viral myocarditis. The diagnosis of myocarditis is dependent in large part on clinical suspicion rather than definitive diagnostic tests.[23] Coxsackie virus is the virus most often associated with myocarditis.[24] An inflammatory drug effect is also possible. The event was reported as resolved despite continued drisapersen treatment.

- DMD114044 Subject 505, a 6 year old male from France, had an SAE coded to the PT Cardiac fibrillation at the end of anesthesia while undergoing elective surgery for transtympanic aerators with sevoflurane as a general anesthetic. He received cardio-

[18] Narrative on ISS p. 3821; Section 5.3.5.3 of the April 27, 2015 submission to NDA 206031.
[19] P. 48 of the STD 2015-012 study report. Link located on p. 72 of the Summary of Clinical Pharmacology.
[20] Subject profile submitted to NDA 206031 on 4/27/2015. No laboratory range of normal values was provided.
[21] Sponsor IR response submitted to NDA 206031 on 10/5/2015.
[22] Sponsor IR response submitted to NDA 206031 on 9/22/2015.
[23] Feldman AM, et al. *N Engl J Med* 2000; 343:1388-1398
[24] Kearny MT, et al. *Postgrad Med J* 2001;77:4-10

respiratory arrest treatment and resuscitation. The event resolved the same day and did not recur. The patient continued treatment with drisapersen for approximately 1 more year.
Reviewer comment: This SAE is unrelated to drisapersen. Cardiac arrhythmias are a known effect of sevoflurane.

Two drisapersen-treated extension study (114349) subjects had SAEs in the Cardiac Disorders SOC. Subjects 597 and 598 both had SAEs coded to the PT Cyanosis.
Reviewer comment: For both Subjects 597 and 598, cyanosis was related to obstructive sleep apnea (related to DMD) and not related to drisapersen.

Gastrointestinal disorders SOC

Four of 285 (1.4%) drisapersen subjects in repeat dose studies had SAEs coded to the Gastrointestinal Disorders SOC (see table below).

Table 8. Serious Adverse Events. Gastrointestinal Disorders SOC. Repeat dose studies. Integrated Summary of Safety analysis.

System Organ Class Preferred Term	Placebo (n = 95)	Drisapersen 6mg/kg (n = 267)	Drisapersen 6mg/kg Intermittent (n = 38)	Drisapersen All Regimens (n = 285)
Gastrointestinal Disorders	1 (1.1%)	4 (1.5%)	0	4 (1.4%)
Diarrhoea	0	1 (0.4%)	0	1 (0.4%)
Enteritis	0	1 (0.4%)	0	1 (0.4%)
Small Intestinal Obstruction	0	1 (0.4%)	0	1 (0.4%)
Vomiting	0	1 (0.4%)	0	1 (0.4%)
Glossitis	1 (1.1%)	0	0	0

Source: Table 6. ISS addendum. Section 5.3.5.3 Sponsor Response submitted to NDA 206031 on 7/24/2015.

In placebo-controlled studies, 2 of 195 (1.0%) drisapersen subjects had an SAE in the Gastrointestinal Disorders SOC, compared to 1 of 95 placebo subjects:[25]

- DMD114044 Subject 1601, a 5 year old male from Turkey, had an SAE coded to the PT Enteritis with nausea and vomiting that started approximately 4 hours after drisapersen dosing. He was hospitalized and given intravenous fluid replacement. The event resolved 7 days later.
  Reviewer comment: This event is possibly related to drisapersen. In placebo-controlled studies, the frequencies of common gastrointestinal and infection-related AEs were generally similar in drisapersen and placebo subjects, except gastroenteritis occurred

[25] Study 114117 placebo subject 2002 had an SAE of glossitis 3 days after the last dose of placebo.

more commonly in drisapersen treated subjects. However, this subject had no gastrointestinal symptoms with other drisapersen doses.

Table 9. On-treatment adverse events (by SOC and preferred term) that occurred in at least 5% of subjects in placebo or drisapersen 6 mg/kg/wk group (placebo-controlled studies)

Adverse event System organ class Preferred term	Placebo N=95 n (%)	Drisapersen 6mg/kg/wk N=161 n (%)
Infections and infestations	**70 (73.7)**	**110 (68.3)**
Nasopharyngitis	30 (31.6)	51 (31.7)
Upper respiratory tract infection	18 (18.9)	20 (12.4)
Gastroenteritis	6 (6.3)	19 (11.8)
Rhinitis	9 (9.5)	15 (9.3)
Influenza	5 (5.3)	10 (6.2)
Pharyngitis	5 (5.3)	6 (3.7)
Ear infection	6 (6.3)	6 (3.7)
Gastrointestinal disorders	**48 (50.5)**	**85 (52.8)**
Vomiting	23 (24.2)	38 (23.6)
Diarrhoea	15 (15.8)	35 (21.7)
Abdominal pain	10 (10.5)	21 (13.0)
Abdominal pain upper	4 (4.2)	12 (7.5)
Constipation	6 (6.3)	10 (6.2)
Nausea	7 (7.4)	8 (5.0)

Source: Sponsor Table 36. Summary of Clinical Safety.

- DMD114117 Subject 3001, a 6 year old male from Australia, had SAEs coded to the PTs Vomiting, Pain in extremity, and Oedema peripheral. After a party in a water park, he had red, swollen and painful calves, vomiting, elevated body temperature of 37.9°C (100.2 °F), and a heart rate of 160 beats per minute (bpm). He received acetaminophen and ondansetron treatment, and all 3 events resolved on the same day.
  Reviewer comment: These SAEs are consistent with heat exhaustion and are unrelated to drisapersen.

Two additional extension study (114349) subjects had SAEs in the Gastrointestinal Disorders SOC:

- Subject 1310, an 8 year old male from Canada, had an SAE coded to the PT Small intestinal obstruction. First drisapersen dose in Study 114044 was August 3, 2011. On Oct. 10, 2011 he had an AE of abdominal pain. He had gastrointestinal AEs intermittently throughout Study 114044 (e.g., abdominal pain, vomiting diarrhea). In Study 114349 (June 10, 2013) he had a partial small bowel obstruction. He underwent endoscopy and colonoscopy under general anesthesia. Biopsies of the duodenum, stomach, distal esophagus, and colon showed non-specific inflammatory changes in the duodenum, possibly drug-related or infectious in nature. No inflammatory changes were noted in the large bowel. Endoscopy revealed evidence of mild esophagitis, gastritis associated with ulceration and erosions, and duodenitis. The gastric erosions were suggested to be secondary to steroid use. There was evidence of moderate patchy colitis in about 1/3 of the colon, suggestive of a diffuse inflammatory or infective process. No evidence of mycoplasmal or mycobacterial infection was noted.

Reviewer comment: This SAE of small bowel obstruction with inflammatory changes is possibly related to drisapersen. There is evidence of increased inflammation with drisapersen in animal studies, as well as in the clinical laboratory data.

- Subject 598, a 17 year old male from Germany who started drisapersen 6 mg/kg/week in March 2011, had SAEs coded to the PTs Diarrhoea and Hypotonia. No history of gastrointestinal symptoms before drisapersen treatment were reported. Twenty eight months after starting drisapersen, he had intermittent, moderate diarrhea for 2 months. Drisapersen was stopped in response to these events. Treatment included loperamide and dimenhydrinate. The events of diarrhea and hypotonia were considered resolved as of 23 August 2013. He did not restart drisapersen, because of proteinuria (8/28/2013 – 9/17/2013). In October 2009, dosing was stopped in all Study DMD114349 subjects.[26] No specific details were provided regarding this subject's hypotonia.
  Reviewer comment: The cause of this subject's diarrhea is unclear. Colonoscopy and gastroscopy, stool cultures, and abdominal ultrasound were negative. No gastrointestinal biopsy results were reported. This case may be consistent with DMD-related chronic intestinal pseudo-obstruction (CIP), which involves fibrosis of the gastrointestinal smooth muscle and can cause episodic gastrointestinal symptoms. Other evidence of DMD-related muscle fibrosis in this subject included cardiac akinesia with MRI suggestive of heart muscle fibrosis in a pattern typical of that seen in DMD (March 2013). In placebo-controlled studies, diarrhea occurred in 22% of drisapersen 6 mg/kg/week subjects, compared to 16% of placebo subjects.[27] A role of drisapersen in this subject's diarrhea is possible.

Nervous System Disorders

Four of 285 (1.4%) subjects in repeat dose studies had SAEs coded to the Nervous System Disorders SOC (see table below).

[26] P. 5 DMD114349 subject 598 subject profile. Submitted to NDA 206031 on 4/27/2015.
[27] Table 36 Summary of Clinical Safety

Table 10. Serious Adverse Events. Nervous System Disorders SOC. Repeat dose studies. Integrated Summary of Safety analysis.

System Organ Class Preferred Term	Placebo (n = 95)	Drisapersen 6mg/kg (n = 267)	Drisapersen 6mg/kg Intermittent (n = 38)	Drisapersen All Regimens (n = 285)
Nervous System Disorders	1 (1.1%)	4 (1.5%)	0	4 (1.4%)
Benign Intracranial Hypertension	0	1 (0.4%)	0	1 (0.4%)
Convulsion	0	1 (0.4%)	0	1 (0.4%)
Hypotonia	0	1 (0.4%)	0	1 (0.4%)
Intracranial Venous Sinus Thrombosis	0	1 (0.4%)	0	1 (0.4%)
Intercostal Neuralgia	1 (1.1%)	0	0	0

Source: Table 6. ISS addendum. Section 5.3.5.3 Sponsor Response submitted to NDA 206031 on 7/24/2015.

In placebo-controlled studies, 2 of 195 (1.0%) drisapersen subjects had an SAE in the Nervous System Disorders SOC, compared to 1 of 95 (1.0%) placebo subjects:

- DMD114044 Subject 1270, a 7 year old male from Brazil had SAEs coded to PTs Intracranial venous sinus thrombosis and Spinal pain. On 12/4/2012, high sensitivity C-reactive protein (hsCRP) was elevated at 9.5 mg/L. On Dec. 11, 2012 (6 months after his first dose of drisapersen), he developed a headache. Over the next few days, he developed seizures, strabismus, and severe thoraco-lumbar pain. A head CT showed hyperattenuating content partially filling the superior sagittal sinus and the straight sinus. Neurological assessment confirmed paralysis of cranial nerve VI (abducens) and signs of thrombosis of venous sinuses. The event of spinal pain was considered resolved on 1 February 2013, and the event of intracranial venous sinus thrombosis was considered resolved with sequelae (paralysis of the VI cranial nerve) on that same date. *Reviewer comment: The cause of this SAE is unclear. Coagulation abnormalities have been reported with DMD.[28] Fibrinogen, aPTT, INR, platelet count, and hemoglobin were normal. Conclusive anti-drisapersen antibody testing was not available.[29] High sensitivity C-reactive protein was elevated 1 week prior to the onset of headache. It is unclear whether drug-related inflammation may have contributed to this event.*

- DMD114044 Subject 576, a 14 year old male from Germany treated with drisapersen 6 mg/kg/week since January 2011, had an SAE coded to the PT Benign intracranial hypertension in July 2015, 2011. After starting drisapersen, he had 6 adverse events of headache (May – July 2011).[30] He had taken deflazacort since 2005. After the diagnosis

[28] Toshio Saito (2014). Coagulation and Fibrinolysis Abnormalities in Patients with Muscular Dystrophy, Fibrinolysis and Thrombolysis, Dr. Krasimir Kolev (Ed.), ISBN: 978-953-51-1265-5, InTech, DOI: 10.5772/57411. Available from: http://www.intechopen.com/books/fibrinolysis-and-thrombolysis/coagulation-and-fibrinolysis-abnormalities-in-patients-with-muscular-dystrophy
[29] P. 48 of the STD 2015-012 study report. Link located on p. 72 of the Summary of Clinical Pharmacology.
[30] Sponsor IR response submitted to NDA 206031 on 9/18/2015.

of intracranial hypertension, he continued drisapersen until the end of Study DMD114349 (last dose January 3, 2014). The event of benign intracranial hypertension ended on April 5, 2013.
Reviewer comment: This SAE may be related to treatment with deflazacort, which he received since 2005. There is a published report of a 9 year old U.S. DMD patient who developed idiopathic intracranial hypertension after starting deflazacort treatment.[31] *However, a contribution of drisapersen to this SAE cannot be ruled out.*

In the extension studies, there were 2 additional drisapersen subjects who had SAEs:

- DMD114673 Subject 105, an 8 year old male from Belgium, who had a seizure (PT Convulsion). On (b) (6), 2 days after his latest dose of drisapersen, he developed a fever of 39.5°C. Four hours later he had a generalized seizure, which lasted 20 minutes. He was hospitalized. Viral swab was positive for H1N1 influenza A. No action was taken with drisapersen treatment.
  Reviewer comment: This subject's seizure is likely related to his fever and H1N1 influenza A infection, which can lead to seizures (with or without fever).[32] *The seizure is consistent with a complex febrile seizure, because of the subject's age and the long seizure duration of 20 minutes. An inflammatory effect (e.g., cerebral vasculitis) of drisapersen contributing to this seizure is possible. Two seizures occurred in drisapersen nonclinical studies.*
- DMD114349 Subject 598, a 17 year old male from Germany, had SAEs coded to the PTs Diarrhoea and Hypotonia.
  Reviewer comment: The reader is referred to the Gastointestinal disorders SOC section of Section 8.4.2 for details of this case.

Musculoskeletal and Connective Tissues Disorders SOC

Four of 285 (1.4%) subjects in repeat dose studies had SAEs coded to the Musculoskeletal and Connective Tissues Disorders SOC (see table below).

[31] Weig SG, et al.. "Idiopathic Intracranial Hypertension in a Child with Duchenne Muscular Dystrophy." Pediatric neurology 45.6 (2011): 406-408.
[32] Pinki,S, et al. "Neurological complications of pandemic influenza A H1N1 2009 infection: European case series and review." European journal of pediatrics 170.8 (2011): 1007-1015.

Table 11. Serious Adverse Events. Musculoskeletal and Connective Tissues Disorders SOC. Repeat dose studies. Integrated Summary of Safety analysis.

System Organ Class Preferred Term	Placebo (n = 95)	Drisapersen 6mg/kg (n = 267)	Drisapersen 6mg/kg Intermittent (n = 38)	Drisapersen All Regimens (n = 285)
Musculoskeletal And Connective Tissue Disorders	0	4 (1.5%)	0	4 (1.4%)
Pain In Extremity	0	1 (0.4%)	0	1 (0.4%)
Scoliosis	0	1 (0.4%)	0	1 (0.4%)
Spinal Pain	0	1 (0.4%)	0	1 (0.4%)
Tendinous Contracture	0	1 (0.4%)	0	1 (0.4%)

Source: Table 6. ISS addendum. Section 5.3.5.3 Sponsor Response submitted to NDA 206031 on 7/24/2015.

In placebo-controlled studies, 2 of 195 (1.0%) drisapersen subjects had an SAE in the Disorders Musculoskeletal and Connective Tissues Disorders SOC, compared to 0 of 95 placebo subjects:

- DMD114117 Subject 3001, a 6 year old male from Australia, had SAEs coded to the PTs Vomiting, Pain in extremity, and Oedema peripheral. (Previously discussed in the Gastrointestinal disorders SOC section.)
  Reviewer comment: These SAEs are consistent with heat exhaustion and are unrelated to drisapersen.

- DMD114044 Subject 1270, a 7 year old male from Brazil had SAEs coded to PTs Intracranial venous sinus thrombosis and Spinal pain.
  Reviewer comment: The reader is referred to the Nervous System Disorders SOC section for discussion of this SAE.

Two extension study (114673) drisapersen subjects had SAEs related to DMD and not related to drisapersen:

- Subject 201 (SAE PT Scoliosis) underwent surgical scoliosis correction.
- Subject 106 (SAE PT Tendinous contracture) underwent tendon retraction release surgery.

Renal and Urinary Disorders SOC

Details of the 4 SAEs coded to the Renal and urinary disorders SOC are discussed in the evaluation of renal toxicity in Section 8.5.2.

General Disorders and Administration Site Conditions SOC

Three of 285 (1.1%) subjects in repeat dose studies had SAEs coded to the General Disorders and Administration Site Conditions SOC (see table below).

Table 12. Serious Adverse Events. General Disorders and Administration Site Conditions SOC. Repeat dose studies. Integrated Summary of Safety analysis.

System Organ Class Preferred Term	Placebo (n = 95)	Drisapersen 6mg/kg (n = 267)	Drisapersen 6mg/kg Intermittent (n = 38)	Drisapersen All Regimens (n = 285)
General Disorders And Administration Site Conditions	0	3 (1.1%)	0	3 (1.1%)
Injection Site Oedema	0	2 (0.7%)	0	2 (0.7%)
Oedema Peripheral	0	1 (0.4%)	0	1 (0.4%)
Pyrexia	0	1 (0.4%)	0	1 (0.4%)

Source: Table 6. ISS addendum. Section 5.3.5.3 Sponsor Response submitted to NDA 206031 on 7/24/2015.

In placebo-controlled studies, there was 1 SAE in this SOC. Study 114117 Subject 3001 had SAEs coded to the PTs Vomiting, Pain in extremity, and Oedema peripheral. (Previously discussed in the Gastrointestinal disorders SOC section.)

In extension study 114349, Subject 125 had SAEs coded to PTs Injection site oedema and Pyrexia, and Subject 511 had an SAE coded to the PT Injection site oedema. These SAEs are discussed in detail in the evaluation of injection site reactions in Section 8.5.3.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

A total of 13 subjects reported AEs that led to permanent treatment discontinuation during the repeat-dose studies, all 13 (4.9%) treated with drisapersen 6 mg/kg/week (see table below). There were no withdrawals in any other treatment groups.

Table 13. Summary of adverse events leading to permanent treatment discontinuation (repeat dose studies)

Adverse event preferred term	Placebo N=95 n (%)	Drisapersen 3mg/kg/wk N=17 n (%)	Drisapersen 6mg/kg/wk N=267 n (%)	Drisapersen 6mg/kg intermittent N=38 n (%)	Drisapersen all regimens N=285 n (%)
Any AE leading to withdrawal	**0**	**0**	**13 (4.9)**	**0**	**13 (4.6)**
Thrombocytopaenia	0	0	8 (3.0)	0	8 (2.9)
Asthenia	0	0	1 (0.4)	0	1 (0.4)
Glomerulonephritis	0	0	1 (0.4)	0	1 (0.4)
Injection site oedema	0	0	1 (0.4)	0	1 (0.4)
Intracranial venous sinus thrombosis	0	0	1 (0.4)	0	1 (0.4)
Proteinuria	0	0	1 (0.4)	0	1 (0.4)
Spinal pain	0	0	1 (0.4)	0	1 (0.4)

Source: Sponsor Table 44

All of the adverse events leading to permanent treatment discontinuation are SAEs discussed elsewhere in this review, except for the AE coded to the PT Asthenia in Study DMD 114349 Subject 520. This subject started treatment in Study 114044 on 5/9/2011. Asthenia was first documented as an AE on 3/28/2012 and was eventually described as severe in August 2012. His

last dose was on 11/14/2012. Additional reasons for discontinuation in this subject were "fear of relapse"…"myalgia, abdominal pain, and lack of efficacy."[33]

I have reviewed the clinical study criteria for stopping treatment.[34] In the opinion of this reviewer, the criteria were appropriate. Additional details will be discussed in the relevant review sections.

8.4.4. Significant Adverse Events

The Sponsor categorized clinical study adverse events by severity (mild, moderate, or severe) in the integrated summary of safety datasets. Most adverse events categorized as severe (and not already included in the serious adverse event assessment) are discussed in Section 8.5 Submission-Specific Safety Issues.

One severe adverse event not discussed elsewhere in this review occurred in Study DMD114876 Subject 203,[35] who had a severe adverse event of a full body rash and hives (PT Urticaria). He started treatment on Aug 1, 2012. He had no prior history of urticaria or medication allergies. He had a severe event of full body rash and hives on Oct. 4, 2012, which was 1 day after drisapersen dosing. No respiratory impairment, cough, wheezing, or angioedema was reported. He was treated with diphenhydramine, and the event was considered resolved on Oct. 9, 2012. He had 2 additional mild episodes of urticaria, which occurred 6 and 165 days after his latest dose of drisapersen. He enrolled in extension study DMD115501 and received 13 doses of drisapersen in April – August 2015 without reported urticaria.
Reviewer comment: This subject had 1 severe episode of urticaria 1 day after drisapersen treatment. He had 2 additional mild episodes of urticaria, which occurred 6 and 165 days after his latest dose of drisapersen. These events are possibly related to drisapersen. It is unclear whether, after the first urticaria event, he received preventive antihistamine medication prior to drisapersen dosing.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Adverse events that occurred in at least 5% of drisapersen subjects in repeat dose studies and more frequently than placebo are summarized in the table below.

[33] Subject 520 narrative. P. 3925 Integrated Summary of Safety.
[34] Summary of Clinical Safety Appendix 8.2.
[35] Narrative submitted to NDA 206031 on 9/21/2015.

Table 14. Summary of adverse events (by system organ class and preferred term) that occurred in at least 5% of drisapersen 6 mg/kg/week subjects (placebo-controlled studies) and greater than placebo

Adverse event System organ class Preferred term	Placebo N=95 n (%)	Drisapersen 6mg/kg/wk N=161 n (%)
Any adverse event	89 (93.7)	158 (98.1)
General disorders and administration site conditions	**44 (46.3)**	**138 (85.7)**
Injection site erythema	8 (8.4)	85 (52.8)
Injection site discolouration	5 (5.3)	56 (34.8)
Pyrexia	22 (23.2)	41 (25.5)
Injection site reaction	2 (2.1)	29 (18.0)
Injection site pain	5 (5.3)	26 (16.1)
Injection site pruritus	1 (1.1)	26 (16.1)
Injection site bruising	9 (9.5)	19 (11.8)
Injection site haematoma	6 (6.3)	14 (8.7)
Injection site induration	1 (1.1)	17 (10.6)
Injection site swelling	0	11 (6.8)
Injection site atrophy	0	9 (5.6)
Injection site urticaria	0	10 (6.2)
Infections and infestations	**70 (73.7)**	**110 (68.3)**
Gastroenteritis	6 (6.3)	19 (11.8)
Influenza	5 (5.3)	10 (6.2)
Gastrointestinal disorders	**48 (50.5)**	**85 (52.8)**
Diarrhoea	15 (15.8)	35 (21.7)
Abdominal pain	10 (10.5)	21 (13.0)
Abdominal pain upper	4 (4.2)	12 (7.5)
Investigations	**28 (29.5)**	**76 (47.2)**
Protein urine present	6 (6.3)	20 (12.4)
Cystatin C increased	4 (4.2)	17 (10.6)
Urine protein/creatinine ratio increased	4 (4.2)	14 (8.7)
Red blood cells urine positive	5 (5.3)	15 (9.3)
Red blood cells urine	5 (5.3)	13 (8.1)
Protein urine	0	8 (5.0)
Injury, poisoning and procedural complications	**47 (49.5)**	**71 (44.1)**
Fall	19 (20.0)	35 (21.7)
Renal and urinary disorders	**26 (27.4)**	**66 (41.0)**
Proteinuria	16 (16.8)	47 (29.2)
Haematuria	5 (5.3)	24 (14.9)
Respiratory, thoracic and mediastinal disorders	**32 (33.7)**	**52 (32.3)**
Epistaxis	6 (6.3)	12 (7.5)
Nasal congestion	3 (3.2)	9 (5.6)
Rhinorrhoea	3 (3.2)	9 (5.6)
Nervous system disorders	**26 (27.4)**	**49 (30.4)**
Headache	20 (21.1)	43 (26.7)
Musculoskeletal and connective tissue disorders	**28 (29.5)**	**38 (23.6)**
Arthralgia	1 (1.1)	11 (6.8)

Source: Sponsor Table 36. Summary of Clinical Safety.

Reviewer comment: I reviewed the adverse events in the drisapersen 3 mg/k/week (N=17) and drisapersen 6 mg/kg/week intermittent (N=38) dose groups. While data is limited because of the small sample sizes in these groups, adverse event frequencies were generally similar in the drisapersen 6 mg/kg/week and 6 mg/kg /week intermittent dose groups. Adverse event frequencies were generally smaller in the drisapersen 3 mg/kg/week group.

Adverse events coded to the SOCs Eye disorders, Psychiatric disorders, Metabolism and nutrition disorders, Ear and labyrinth disorders occurred less frequently in drisapersen subjects, compared to placebo subjects.

Analyses were performed to combine the frequencies of split terms related to renal toxicity.[36] In placebo-controlled studies, proteinuria[37] occurred in 70 of 161 (43.5%) drisapersen 6 mg/kg/week subjects, compared to 22 of 95 (23.2%) placebo subjects. Hematuria[38] occurred in 26 of 161 (16.1%) drisapersen 6 mg/kg/week subjects, compared to 10 of 95 (10.5%) placebo subjects.

Analyses were performed to combine the frequencies of split terms for injection site reactions.[39] In placebo-controlled studies, skin discoloration[40] occurred in 58 of 161 (36.0%) drisapersen 6 mg/kg/week subjects, compared to 7 of 95 (7.4%) placebo subjects. Chronic skin damage[41] occurred in 19 of 161 (11.8%) drisapersen 6 mg/kg/week subjects, compared to 1 of 95 (1.1%) placebo subjects. Ulceration[42] occurred in 5 of 161 (3.7%) drisapersen 6 mg/kg/week subjects, compared to 0 of 95 placebo subjects. Injection site hair growth[43] occurred in 10 of 161 (6.2%) drisapersen 6 mg/kg/week subjects, compared to 0 of 95 placebo subjects.

The following categories of common events are discussed in detail in Section 8.5 Analysis of Submission-Specific Safety Issues, including thrombocytopenia, renal toxicity, injection site reactions, and inflammatory biomarkers.

Arthralgia was reported in 11 of 161 (6.8%) drisapersen 6 mg/kg/week subjects, compared to 1 of 95 (1.1%) placebo subjects.

In repeat dose studies, alopecia was reported in 13 out of 285 (4.6%) drisapersen subjects.

[36] Table 1. ISS addendum submitted to NDA 206031 on 09/25/2015.
[37] Adverse events with PTs Proteinuria, Protein urine present, and Protein urine were combined. Subjects with adverse events coded to more than 1 of the 3 terms and were counted once.
[38] Hematuria-- Subjects had an adverse event coded to at least one of these Preferred Terms: Red blood cells urine positive, or Red blood cells urine
[39] Table 2. ISS addendum submitted to NDA 206031 on 09/25/2015.
[40] Skin discoloration -- Subjects had an injection site reaction adverse event coded to at least one of these Preferred Terms: Injection site discoloration, Pigmentation disorder, Skin hyperpigmentation, or Skin discoloration.
[41] Chronic skin damage -- Subjects had an injection site reaction adverse event coded to at least one of these Preferred Terms: Atrophy, Fat tissue decreased, Injection site nodule, Hypertrophy, Plaque, Calcification, Scar, Mass, Acquired lipodystrophy, or Skin fibrosis.
[42] Ulceration -- Subjects had an injection site reaction adverse event coded to at least one of these Preferred Terms: Injection site vesicles, Application site vesicles, Injection site erosion, Injection site ulcer, or Injection site scab
[43] Hair growth -- Subjects had an injection site reaction adverse event coded to at least one of these Preferred Terms: Hair growth, Hypertrichosis, or Hirsutism at injection site.

The sponsor proposes to include a table in the label in which AEs for drisapersen occurred in at least 5% of subjects and at least twice the placebo rate.

Reviewer comment: In the opinion of this reviewer, the Sponsor's plan to include a table in the label in which AEs for drisapersen occurred in at least 5% of subjects and at least twice the placebo rate is acceptable. This threshold includes the common adverse events of clinical importance.

8.4.6. **Laboratory Findings**

Hematology

Mean baseline values and mean changes at Weeks 24 and 48 in placebo-controlled studies are summarized in the table below. Decreases in hemoglobin, hematocrit, leukocytes, neutrophils, erythrocytes and reticulocytes were greater with drisapersen than with placebo; however, the size of these decreases was small.

At 48 weeks, the mean change in platelet count was -67.1 x 10^9/L in drisapersen 6 mg/kg/week subjects, compared to -8.7 x 10^9/L in placebo subjects.

Reviewer comment: No cases of immune thrombocytopenia were diagnosed in placebo-controlled studies. No post-treatment platelet levels < 75 x 10^9/L occurred in placebo-controlled studies. *The decreases in platelet count seen in placebo-controlled studies may have occurred via a different mechanism, which is unclear at this time.*

One subject, treated with drisapersen 6 mg/kg/week intermittent had a shift from Grade 1 to Grade 2 for decreased hemoglobin[44] at Weeks 12 and 24. No other shifts to Grade 2, 3 or 4 were observed for hemoglobin. One subject, treated with drisapersen 3 mg/kg/week had a decrease in leukocytes[45] from normal to Grade 2 at Week 24. No other shifts to Grade 2, 3 or 4 were observed for leukocytes. The percentages of subjects with shifts in lymphocytes and neutrophils were similar for placebo and drisapersen.

[44] Reported as anaemia in ISS Table 11.81.
Hemoglobin CTCAE Grade Ranges in G/L Units: 0: ≥LLN; 1: ≥100 - <LLN; 2: ≥ 80 - <100; 3: ≥65 - <80; 4: <65.
[45] Leukocytes CTCAE Grade Ranges in x 10^9/L Units: 0: ≥LLN; 1: ≥3.0 - <LLN; 2: ≥ 2.0 - < 3.0; 3: ≥ 2.0 - < 1.0; 4: <1.0.

Table 15. Summary of hematology parameters: Baseline mean (SD) and mean (SD) changes from baseline at Weeks 24 and 48 (placebo-controlled studies)

	Placebo N=95		Drisapersen 3 mg/kg/wk N=17		Drisapersen 6 mg/kg/wk N=161		Drisapersen 6 mg/kg intermittent [a] N=17		Drisapersen all regimens N=195	
Haemoglobin, g/L										
Baseline mean (SD)	n=95	136.8 (11.48)	n=17	138.9 (11.77)	n=161	137.5 (9.34)	n=17	134.5 (12.06)	n=195	137.4 (9.82)
Week 24: Mean (SD) change	n=93	-1.0 (7.57)	n=15	-7.3 (7.02)	n=157	-3.8 (7.75)	n=16	-6.9 (7.84)	n=188	-4.3 (7.77)
Week 48: Mean (SD) change	n=76	0.4 (7.72)	NA	NA	n=137	-5.2 (7.67)	n=14	-3.4 (12.08)	n=151	-5.0 (8.22)
Haematocrit, ratio										
Baseline mean (SD)	n=95	0.4121 (0.03533)	n=17	0.4161 (0.03897)	n=161	0.4144 (0.02988)	n=17	0.4062 (0.03441)	n=195	0.4139 (0.03107)
Week 24: Mean (SD) change	n=93	-0.0037 (0.02554)	n=15	-0.0220 (0.02802)	n=157	-0.0161 (0.02604)	n=16	-0.0234 (0.02404)	n=188	-0.0172 (0.02602)
Week 48: Mean (SD) change	n=76	0.0029 (0.02405)	NA	NA	137	-0.0187 (0.02656)	n=14	-0.0186 (0.03587)	n=151	-0.0186 (0.02741)
Lymphocyte count, GI/L										
Baseline mean (SD)	n=95	2.666 (1.3183)	n=17	2.257 (1.0164)	n=161	2.888 (1.2599)	n=17	2.434 (1.1758)	n=195	2.793 (1.2460)
Week 24: Mean (SD) change	n=92	0.077 (1.4650)	n=15	0.282 (1.2126)	n=156	-0.507 (1.2663)	n=15	-0.421 (1.5440)	n=186	-0.437 (1.2966)
Week 48: Mean (SD) change	n=75	0.009 (1.13169)	NA	NA	n=136	-0.552 (1.1630)	n=14	-0.215 (1.0104)	n=150	-0.520 (1.1507)
Neutrophil count, GI/L										
Baseline mean (SD)	n=95	5.580 (2.8535)	n=17	6.620 (2.4867)	n=161	5.459 (2.6390)	n=17	5.154 (2.3110)	n=195	5.534 (2.6105)
Week 24: Mean (SD) change	n=92	-0.513 (3.1363)	n=15	-1.966 (2.6005)	n=156	-1.149 (2.5595)	n=15	-1.099 (2.3155)	n=186	-1.211 (2.5410)
Week 48: Mean (SD) change	n=75	-0.614 (2.8493)	NA	NA	n=136	-1.314 (2.5129)	n=14	-1.300 (3.2791)	n=150	-1.313 (2.5806)
Thrombocyte count, GI/L										
Baseline mean (SD)	n=95	306.4 (64.78)	n=17	311.5 (64.52)	n=161	309.5 (68.75)	n=17	277.5 (95.28)	n=195	306.9 (71.23)
Week 24: Mean (SD) change	n=92	-1.3 (49.62)	n=16	-44.8 (44.94)	n=157	-49.8 (52.89)	n=17	-27.8 (115.75)	n=190	-47.4 (60.36)
Week 48: Mean (SD) change	n=73	-8.7 (37.61)	NA	NA	n=136	-67.1 (54.58)	n=14	-20.0 (100.22)	n=150	-62.7 (61.35)
Erythrocyte count, TI/L										
Baseline mean (SD)	n=95	4.78 (0.389)	n=17	4.72 (0.388)	n=161	4.76 (0.338)	n=17	4.71 (0.364)	n=195	4.75 (0.343)
Week 24: Mean (SD) change	n=93	0.00 (0.291)	n=15	-0.21 (0.260)	n=157	-0.16 (0.279)	n=16	-0.22 (0.254)	n=188	-0.17 (0.275)
Week 48: Mean (SD) change	n=76	0.05 (0.284)	NA	NA	n=137	-0.27 (0.290)	n=14	-0.26 (0.388)	n=151	-0.27 (0.299)
Reticulocyte count, TI/L										
Baseline mean (SD)	n=95	0.06821 (0.032167)	n=17	0.08152 (0.033182)	n=161	0.06667 (0.029584)	n=17	0.06632 (0.33939)	n=195	0.06793 (0.030420)
Week 24: Mean (SD) change	n=92	-0.00508 (0.028806)	n=15	-0.01903 (0.026295)	n=156	-0.01299 (0.028599)	n=16	-0.01431 (0.032650)	n=187	-0.01359 (0.028677)
Week 48: Mean (SD) change	n=76	-0.00742 (0.026653)	NA	NA	n=137	-0.016667 (0.025619)	n=14	-0.01773 (0.034990)	n=151	-0.01677 (0.026481)
Leukocyte count, GI/L										
Baseline mean (SD)	n=95	8.69 (2.782)	n=17	9.31 (2.252)	n=161	8.82 (2.663)	n=17	8.06 (2.334)	n=195	8.80 (2.606)
Week 24: Mean (SD) change	n=92	-0.39 (3.157)	n=15	-1.69 (2.803)	n=156	-1.61 (2.700)	n=15	-1.55 (2.665)	n=186	-1.61 (2.691)
Week 48: Mean (SD) change	n=75	-0.59 (2.647)	NA	NA	n=136	-1.83 (2.613)	n=14	-1.42 (3.435)	n=150	-1.79 (2.689)

Clinical chemistry laboratory results

In placebo-controlled studies, data were available for the following electrolytes: sodium, phosphate, calcium, and potassium. Mean changes in these electrolytes were similar in drisapersen and placebo subjects.

Reviewer comment: No serum bicarbonate measurements were available for analysis. This laboratory parameter is of interest, because of drisapersen accumulation in the proximal tubule and the renal toxicity associated with drisapersen. There were no blood acid-base disorders reported as adverse events in the clinical development program.

In placebo-controlled studies, there were no shifts from CTCAE[46] Grade 0 or Grade 1 at baseline to Grade 2, 3 or 4 for hyponatraemia,[47] hyperkalaemia,[48] hypophosphataemia,[49] hypocalcemia,[50] and hypercalcaemia.[51]

Similar frequencies of hypernatremia, categorized by CTCAE grade, occurred in drisapersen and placebo subjects (see table below).

Table 16. Hypernatremia. Shifts from baseline to worst post-treatment value in hypernatremia by CTCAE grade. Placebo-controlled studies.

	Baseline CTCAE Grade					
Laboratory Test Name / Treatment Group / Worst Post-Treatment CTCAE Grade	0	1	2	3	4	Total
Hypernatremia (sodium)						
Placebo (n=95)						
0	83 (87.4%)	0	0	0	0	83
1	9 (9.5%)	0	0	0	0	9
2	1 (1.1%)	0	0	0	0	1
3	2 (2.1%)	0	0	0	0	2
4	0	0	0	0	0	0
Total	95	0	0	0	0	95
6 mg/kg/week Drisapersen (n=162)						
0	135 (83.3%)	0	0	0	0	135
1	12 (7.4%)	1 (0.6%)	0	0	0	13
2	8 (4.9%)	1 (0.6%)	1 (0.6%)	0	0	10
3	3 (1.9%)	0	0	0	0	3
4	1 (0.6%)	0	0	0	0	1
Total	159	2	1	0	0	162

Source: Sponsor Table 10.1. ISS addendum submitted to NDA 206031 on July 20, 2015.

Reviewer comment: The etiology of hypernatremia cases was not discussed in the NDA submission. Hypernatremia can occur with DMD-associated exertional rhabdomyolysis.[52]

[46] Common Terminology Criteria for Adverse Events (CTCAE) v4.0. NIH publication # 09-7473. May 29, 2009.
[47] Hyponatremia CTCAE Grade Ranges in mmol/L Units: 0: ≥LLN; 1: ≥130 - <LLN; 2:N/A; 3: ≥120 - <130; 4: <120.
[48] Hyperkalemia CTCAE Grade Ranges in mmol/L Units: 0: <ULN; 1: >ULN - 5.5; 2: >5.5 – 6.0; 3: > 6.0 – 7.0; 4:> 7.0.
[49] Hypophosphatemia CTCAE Grade Ranges in mmol/L Units: 0: ≥LLN; 1: ≥0.8 - <LLN; 2:≥0.6 – <0.8; 3: ≥0.3 - <0.6; 4: <0.3.
[50] Hypocalcemia CTCAE Grade Ranges in mmol/L Units: 0: ≥LLN; 1: ≥2.0 - <LLN; 2:≥1.75 – <2.0; 3: ≥1.5 - <1.75; 4: <1.5.
[51] Hypercalcemia CTCAE Grade Ranges in mmol/L Units: 0: <ULN; 1: >ULN – 2.9; 2: >2.9 – 3.1; 3: > 3.1 – 3.4; 4:> 3.4.

Laboratory findings related to the following adverse events of special interest are discussed in Section 8.5:

- Renal toxicity
- Thrombocytopenia
- Hepatic toxicity
- Coagulation abnormalities
- Inflammation

Reviewer comment: Apart from results associated with drisapersen adverse events of special interest (listed above), laboratory results were generally similar for drisapersen and placebo subjects.

8.4.7. **Vital Signs**

In placebo-controlled studies, categorical analyses of changes in vital signs from baseline were calculated at Weeks 12, 24, 36, and 48.[53] Results were similar for drisapersen and placebo subjects at each time point. The table below displays changes in vital signs from baseline to Week 48. Analyses of baseline vital signs data and changes from baseline at Weeks 12, 24, 36, and 48 were also similar for drisapersen and placebo subjects.

[52] Figarella-Branger, D., et al. "Exertional rhabdomyolysis and exercise intolerance revealing dystrophinopathies." *Acta neuropathologica* 94.1 (1997): 48-53.

[53] ISS Table 11.84

Table 17. Frequency of categorical changes in vital signs from baseline to Week 48. Placebo-controlled studies.

Study Visit Vital Signs, unit Changes Compared to Baseline	Placebo (N=95)	3 mg/kg/week Drisapersen (N=17)	6 mg/kg/week Drisapersen (N=161)	6 mg/kg Drisapersen Intermittent - 9 doses in 10 week cycle (N=17)	Any Drisapersen (N=195)
Week 48					
Systolic Blood Pressure (SBP), mm Hg					
n	78	N/A	137	15	152
SBP increment > 20 mm Hg	5 (6.4%)		7 (5.1%)	1 (6.7%)	8 (5.3%)
SBP increment > 40 mm Hg	0		1 (0.7%)	0	1 (0.7%)
SBP decrement > 20 mm Hg	2 (2.6%)		6 (4.4%)	1 (6.7%)	7 (4.6%)
SBP decrement > 40 mm Hg	0		0	0	0
Diastolic Blood Pressure (DBP), mm Hg					
n	78	N/A	137	15	152
DBP increment > 10 mm Hg	11 (14.1%)		18 (13.1%)	3 (20.0%)	21 (13.8%)
DBP increment > 20 mm Hg	4 (5.1%)		5 (3.6%)	0	5 (3.3%)
DBP decrement > 10 mm Hg	9 (11.5%)		21 (15.3%)	1 (6.7%)	22 (14.5%)
DBP decrement > 20 mm Hg	1 (1.3%)		3 (2.2%)	0	3 (2.0%)
Heart Rate (HR), bpm					
n	78	N/A	137	15	152
HR increment > 15 bpm	12 (15.4%)		19 (13.9%)	1 (6.7%)	20 (13.2%)
HR increment > 30 bpm	3 (3.8%)		5 (3.6%)	0	5 (3.3%)
HR decrement > 15 bpm	12 (15.4%)		13 (9.5%)	3 (20.0%)	16 (10.5%)
HR decrement > 30 bpm	2 (2.6%)		1 (0.7%)	1 (6.7%)	2 (1.3%)
Temperature, °C					
n	60	N/A	119	N/A	119
Temperature > 38.0 C	0		0		0

Source: ISS Table 11.84

8.4.8. **Electrocardiograms (ECGs)**

Characteristics of ECG testing in the drisapersen clinical development program are summarized in the table below.

Table 18. Characteristics of ECG testing in the drisapersen clinical development program

Study	Number of subjects with at least 1 post-treatment ECG	Schedule of ECG Assessment (baseline and post-treatment)	Number of scheduled ECG assessments	ECG readers blinded to treatment assignment (Y/N/NA)	ECG reading method (e.g., cardiologist, automatic reading)
DMD114044	186	Week 0(baseline), 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48	13	Y	Automatic reader was used unless values were reported as 'abnormal' at which point the ECG was read by a cardiologist or a person trained in assessments of ECGs
DMD114117	53	Week 1(baseline), 3, 5, 7, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49	15	Y	Same
DMD114876	51	Week 0(baseline), 4, 8, 12, 24	5	Y	Same
PRO-051-02	12	Week 1 (baseline), 5, 18	3	N	Same
DMD114673	12	Treatment beyond core study period: Every 4 weeks for the first 85 weeks, and then, every cycle consisting of 4 weeks, 5 weeks, and 3 weeks until week 193, and Week 191, 194, 196, 197, 199, 200, 202, 203, 205, 209, 214, 217.		N	Same
DMD114349	233	Week 0 (baseline), 24, 48, 72, 104	5	N	Same

Source: P. 6 Sponsor submission to NDA206031 on 9/25/2015

The table below summarizes QT values corrected according to Bazett's formula[54] (QTcB) in placebo-controlled studies. Thirty of 161 (18.6%) of drisapersen 6 mg/kg/week subjects had a maximum change in QTcB from baseline >30 to ≤ 60 milliseconds (msec), compared to 16 of 95 (16.8%) placebo subjects. Eighteen of 161 (11.2%) of drisapersen 6 mg/kg/week subjects had a maximum change in QTcB from baseline >60 msec, compared to 9 of 95 (9.5%) placebo subjects. An automatic reader was used, unless values were reported as 'abnormal,' at which point the ECG was read by a cardiologist or a person trained in assessments of ECGs.

[54] Post-treatment changes in heart rate from baseline were similar in drisapersen subjects, compared to placebo subjects.

Table 19. Summary of graded QTcB and change in QTcB (placebo-controlled studies)

Timepoint	Range (msec)	Placebo N=95 n (%)	Drisapersen 6 mg/kg/wk N=161 n (%)
QTcB value			
Baseline	n	95 (100)	159 (98.8)
	≤450	93 (97.9)	155 (96.3)
	>450 and ≤480	2 (2.1)	2 (1.2)
	>480 and ≤500	0	2 (1.2)
	>500	0	0
Maximum on treatment	n	95 (100)	161 (100)
	≤450	77 (81.1)	124 (77.0)
	>450 and ≤480	15 (15.8)	34 (21.1)
	>480 and ≤500	3 (3.2)	3 (1.9)
	>500	0	0
Increase in QTcB from baseline			
Maximum on treatment	n	80 (84.2)	143 (88.8)
	0 to ≤30	55 (57.9)	95 (59.0)
	>30 to ≤60	16 (16.8)	30 (18.6)
	>60	9 (9.5)	18 (11.2)

Source: Summary of Clinical Safety Table 91

The table below summarizes QT values corrected according to Friedericia's formula (QTcF) in placebo-controlled studies. Thirty one of 161 (19.3%) of drisapersen 6 mg/kg/week subjects had a maximum change in QTcB from baseline >30 to ≤ 60 milliseconds (msec), compared to 13 of 95 (13.7%) placebo subjects. Fourteen of 161 (8.7%) of drisapersen 6 mg/kg/week subjects had a maximum change in QTcB from baseline >60 msec, compared to 7 of 95 (7.4%) placebo subjects.

Table 20. Summary of change in QTcF (placebo-controlled studies)

	Range (msec)	Placebo (N=95) n (%)	6 mg/kg/wk (N=161) n (%)
Maximum on-treatment value [1]	n	82 (86.3)	144 (89.4)
	0 - <=30	62 (65.3)	99 (61.5)
	>30 and <=60	13 (13.7)	31 (19.3)
	>60	7 (7.4)	14 (8.7)

Source: ISS Table 11.68

In Study DMD114876, 12-lead Holter monitoring was performed on all subjects, and Holter ECGs were read by a central cardiologist blinded to study treatment. Evaluation of QTcB showed that mean changes were small for all treatment groups (drisapersen 3 mg/kg/week, drisapersen 6 mg/kg/week, and placebo), and there was no clear dose response relationship and no clear difference from placebo. Outlier analyses at Week 24 showed no subjects with QTcB >480 msec in any group and no subjects with QTcB >450 msec in the drisapersen 6 mg/kg/week group. There were no changes from baseline of >60 msec and one change of 30 to 60 msec in the group receiving drisapersen 6 mg/kg/week (see table below).

Table 21. Summary of Outlier Analysis of Holter ECG Data from Study DMD114876

	Number (%) of Subjects		
	Placebo (combined) (N=16)	Drisapersen 3mg/kg/week (N=17)	Drisapersen 6mg/kg/week (N=18)
n [a]	15	15	18
Any event	**4 (27)**	**3 (20)**	**4 (22)**
Heart rate <50 bpm and ≥25% decrease from baseline	0	0	0
Heart rate >100 bpm and ≥25% increase from baseline	3 (20)	2 (13)	3 (17)
PR interval >200 msec and ≥25% increase from baseline	0	0	0
QRS interval >100 msec and ≥25% increase from baseline	0	0	0
QT interval >500 msec and baseline QT interval ≤500 msec	0	0	0
QTcF interval >500 msec and baseline QTcF interval ≤500 msec	0	0	0
QTcF interval >480 msec and baseline QTcF interval ≤480 msec	0	0	0
QTcF interval >450 msec and baseline QTcF interval ≤450 msec	0	0	0
QTcF interval change from baseline 30-60 msec	0	1 (7)	1 (6)
QTcF interval change from baseline >60 msec	0	0	0
QTcB interval >500 msec and baseline QTcB interval ≤500 msec	0	0	0
QTcB interval >480 msec and baseline QTcB interval ≤480 msec	0	0	0
QTcB interval >450 msec and baseline QTcB interval ≤450 msec	1 (7)	1 (7)	0
QTcB interval change from baseline 30-60 msec	0	0	1 (6)
QTcB interval change from baseline >60 msec	0	0	0

Source: Table 53 Study DMD114876 Clinical Study Report
a. Subjects with a baseline assessment and at least one on-treatment assessment.
For Heart Rate, baseline assessments were those within a 30 minute time period from, and closest in time to the corresponding Week 23 assessments (regardless of heart rate).
For PR, QRS, QT, QTcF and QTcB, baseline assessments were those within a 30 minute time period from, and with the closest heart rate to, and within 10 BPM of the corresponding Week 23 assessments.

There were no reports of torsade de pointes or ventricular tachycardia in the drisapersen clinical development program. One case of cardiac fibrillation (DMD114044 Subject 505) occurred while undergoing elective surgery for transtympanic aerators with sevoflurane as a general anesthetic; no QT prolongation was reported in this case. DMD114673 Subject 105 had a seizure in the setting of H1N1 influenza A infection and fever; no QT prolongation was reported in this case.

8.4.9. QT

No thorough QT study has been performed with drisapersen.

Reviewer's comment: In ECG measurements (read by an automatic reader unless reported as 'abnormal'), increases in QTcB and QTcF from baseline were more frequent in drisapersen subjects, compared to placebo subjects. However, in Study DMD114876 QTcB readings from Holter ECGs (read by a central cardiologist blinded to treatment) showed no clear dose response relationship and no clear difference from placebo. In nonclinical studies, drisapersen did not affect the potassium outward current in Chinese hamster ovary (CHO) cells transfected with

hERG cDNA.[55] This is consistent with the lack of alteration of ion channel function seen with other members of the phosphorothioate oligonucleotide class.[56] Given that oligonucleotides are polyanionic molecules of large molecular weight, alteration of ion channel function is less likely. At this time, there is no nonclinical or strong clinical evidence of an adverse effect on the QT interval. The Division of Cardiovascular and Renal Products will be consulted.

8.4.10. **Immunogenicity**

Plasma samples obtained for pharmacokinetic measurements in clinical study DMD114044 were analyzed for anti-drug antibody (ADA) presence (titled Study 2015-012). A total of 109 subjects treated with drisapersen and 50 subjects who received placebo could be conclusively analyzed.

Reviewer comment: Subjects with no week 47/48 plasma sample available for ADA testing were categorized as Anti-drug antibody (ADA) inconclusive (14 drisapersen subjects and 8 placebo subjects). Subjects 527 (SAE Glomerulonephritis) and 1270 (SAE Intracranial venous sinus thrombosis) discontinued Study 114044 early and had inconclusive ADA results (i.e., no positive ADA test and no testing at Week 47/48).[57]

In 29.4% (32 out of 109 subjects) of the treated evaluable subjects, ADAs were detected.[58] Overall, median titers increased with prolonged treatment. Median titers ranging from 50–300 at Weeks 8 to 24, and were 1000 and 800 at Weeks 36 and 48, respectively.[59] All placebo samples were negative, except for one subject who was considered a likely false positive.[60]

Reviewer comment: Overall, median titers increased with longer durations of exposure. There may be an increasing risk of adverse events related to immunogenicity with longer exposure to

[55] P. 12 Nonclinical Overview. Submitted to NDA 206031 on 10/10/2014.
[56] Henry SP, et al. "Toxicologic properties of 2′ O-methoxyethyl chimeric antisense inhibitors in animals and man." Antisense drug technology: principles, strategies and applications. CRC, Boca Raton, FL (2007): 327-364.
[57] According to the Sponsor (submitted 9/21/2015): "There were no positive anti-drisapersen antibody test results for DMD114044 Subject 527 or Subject 1270. Testing was performed at Week 24 for Subject 527 and at Week 8, 12, and 24 for Subject 1270. The SAE Glomerulonephritis for Subject 527 occurred 29 weeks after start of the treatment and SAE Intracranial venous sinus thrombosis for Subject 1270 occurred 25 weeks after start of treatment."
[58] Section 4.1.1. Summary of Clinical Pharmacology. Submitted to NDA 206031 on 4/27/2015.
[59] Sponsor Table 12. P. 40 Summary of Clinical Pharmacology.
[60] For one placebo subject the first sample obtained was positive (titer of 200) at Week 0, whereas all subsequent samples from this subject were negative, indicating a likely false positive.

drisapersen. Immunogenicity data from extension study DMD114349 have been collected, but Sponsor analyses were ongoing at the time of this review.[61]

Study 2015-012 did not demonstrate a difference between ADA positive and ADA negative subjects with regard to demographics or rates of SAEs, adverse events of special interest (AESIs) and AEs that occurred in at least 5% of subjects) and laboratory parameters (thrombocyte count, high sensitivity C-reactive protein (hsCRP), urine protein excretion, serum cystatin C, urine cystatin C, alanine transferase (ALT), glutamate dehydrogenase (GLDH) and total bilirubin) and muscle distribution.

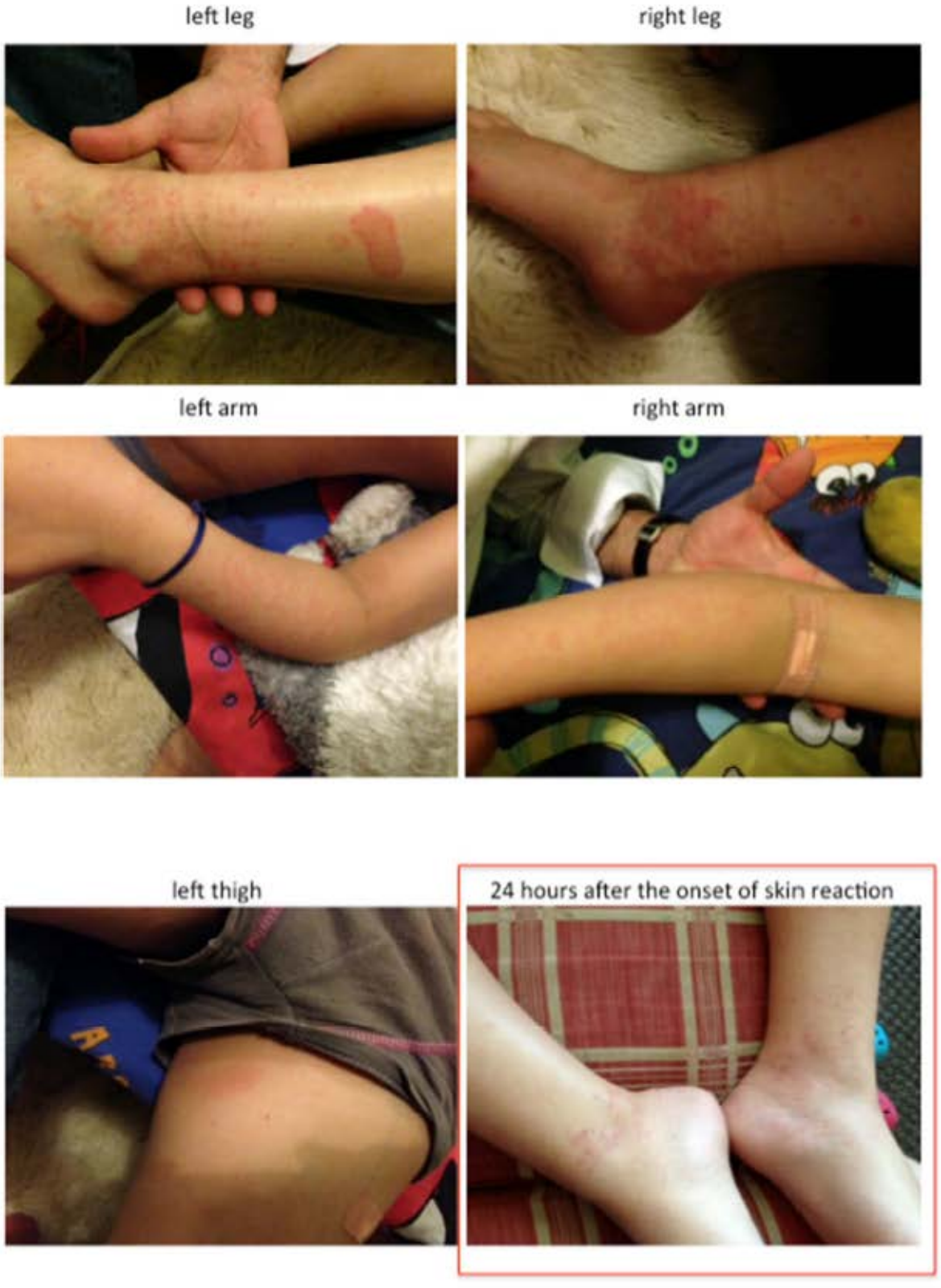
Reviewer comment: Study 2015-012 did not have an adequate number of subjects to make conclusions regarding rare adverse events and serious adverse events. The study analysis included 3 SAEs in drisapersen 6 mg/kg/week subjects and 4 in placebo subjects.

Study DMD114349 subject 2026, a 6 year old male from France, had an adverse event coded to PT Henoch-Schonlein purpura with concomitant positive anti-drisapersen IgG antibodies.[62] He started treatment with 6 mg/kg/week drisapersen in Study DMD114349 on November 2, 2011. Starting on October 2, 2012 (Week 48), the subject tested positive for anti-drisapersen IgG; an additional positive test for IgG occurred on 22 January 2013 (Week 64).

Starting in April 2013, he had multiple episodes of fatigue, weakness, feeling cold, and pallor approximately 1 hour after drisapersen dosing. These episodes resolved spontaneously after about 1 hour. On June 11, 2013, he had a reaction similar to his previous post-administration symptoms. He had an elevated pulse (112 bpm) and normal blood pressure and temperature. He complained of pain in the left thigh, above the injection site. Six hours after drisapersen administration, he developed a skin reaction on his legs, thighs, arms, and abdomen. Photographs of the rash 6 hours (the first 5 pictures) and 24 hours (the 6th picture) after the June 11, 2013 injection are provided below.

[61] Sponsor response submitted to NDA 206031 on 9/21/2015.
[62] ISS addendum. Submitted to NDA 206031 on 8/29/2015.

Figure 2. DMD114349 Subject 2026. AE PT Henoch-Schonlein purpura. Rash 6 and 24 hours after June 11, 2013 Injection



On June 16, 2013 he saw his pediatrician, who reported a Henoch-Schönlein-like purpural rash on the lower limbs, along with mild pharyngitis and conjunctivitis. No events of abdominal pain, arthritis, or arthralgia were reported with the rash. His next dose, on (b) (6), was administered during an overnight hospitalization, because his post-administration symptoms had become worse. He developed a rash on his lower extremities, 3 days after dosing, which he had (b) (6). He received no additional drisapersen doses. According to the Sponsor, all dosing in Study DMD114349 was put on hold in September 2013.

Laboratory results during the study were as follows:

Table 22. DMD114349 Subject 2026. Laboratory results.

Date	Complement C3	C-reactive protein	Platelets	Cystatin C	Creatinine	Urine Protein	Urine RBC
	0.9-1.8 g/L	mg/L	130-400 GI/L	0.6-0.8 mg/L	33.6-64.5 µmol/L	mg/L	
2 November 2011 (Baseline)	1.41	0.3	371	0.6	14.7	83	None
20 March 2012	1.29	0.3	416	0.6	NR	99	None
2 October 2012	1.3	0.5	317	0.8	21.5	122	None
19 March 2013	1.44	0.6	338	0.9	20.4	52	None
14 May 2013	0.97	1.1	352	0.9	16.8	208	5-10
9 July 2013	0.93	1.2	231	0.9	18.5	51	None
3 September 2013	0.83	2.2	277	0.8	20.2	119	None
29 October 2013	1.21	0.4	293	0.8	17.5	50	None

Source: ISS addendum. Submitted to NDA 206031 on 8/29/2015.

No biopsy data related to this AE is available.

Reviewer comment: This AE coded to the PT Henoch-Schonlein purpura, an antibody-related disease, is related to drisapersen. This subject had concurrent positive anti-drisapersen IgG antibodies. No biopsy data are available.

Oligonucleotides are designed to be structurally related to nucleic acids, especially DNA. Thus, antibodies to an oligonucleotide can cross-react with endogenous DNA, especially circulating DNA. DNA is present in the blood of normal individuals, and levels can rise in disease states characterized by inflammation or cell injury and death, such as DMD. One potential mechanism of pathogenesis with anti-oligonucleotide antibodies, such as anti-drisapersen antibodies, is the

formation of immune complexes which can deposit into tissues such as the kidney or blood vessels.[63]

Reviewer conclusion: Immunogenicity occurred in 29.4% of drisapersen subjects with evaluable plasma samples. The currently available information is insufficient to describe the effects of anti-drisapersen antibodies, especially in regards to rare adverse events and serious adverse events.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Thrombocytopenia

In placebo-controlled studies, mild thrombocytopenia occurred more frequently in drisapersen subjects, compared to placebo subjects. In placebo-controlled studies, 16 of 161 (9.9%) drisapersen 6 mg/kg/week subjects had a platelet count below the lower limit of normal and ≥ 75 x 10^9/L (the level below which primary hemostasis is generally considered to be impaired), compared to 3 of 95 (3.2%) placebo subjects. No subjects (in any treatment group) had treatment-emergent platelet levels < 75 x 10^9/L in placebo-controlled studies.[64]

While only mild thrombocytopenia occurred in placebo-controlled studies, serious thrombocytopenia occurred with drisapersen in the extension studies. In extension studies, eight of 267 (3.0%) drisapersen 6 mg/kg/week subjects had a thrombocytopenia serious adverse event (see table below).

Table 23. Summary of on-treatment thrombocytopenia events (repeat dose studies)

Adverse event	Placebo N=95 n (%)	Drisapersen 3mg/kg/wk N=17 n (%)	Drisapersen 6mg/kg/wk N=267 n (%)	Drisapersen 6mg/kg interm ttent[a] N=38 n (%)	Drisapersen all regimens[b] N=285 n (%)
Any thrombocytopaenia event	0	0	19 (7.1)	2 (5.3)	20 (7.0)
Any thrombocytopaenia SAE	0	0	8 (3.0)	0	8 (2.8)
Any severe thrombocytopaenia event	0	0	7 (2.6)	0	7 (2.5)

Source: Sponsor Table 71. Summary of Clinical Safety p. 145.
[a] Intermittent includes subjects dosed with 9 doses in a 10-week cycle
[b] Subjects treated with more than one drisapersen regimen are only counted once in this group.
Table includes studies DMD114117, DMD114044, DMD114876, DMD114349, PRO051-02, and DMD114673.

Six subjects had thrombocytopenia <20 x 10^9/L. Drisapersen subjects had symptoms of bleeding that included hematemesis, epistaxis, petechiae, and gingival bleeding. Patients with

[63] Wang, Jian, et al. "Oligonucleotide-Based Drug Development Considerations for Clinical Pharmacology and Immunogenicity." Therapeutic Innovation & Regulatory Science (2015).
[64] P. 80 ISS addendum submitted to NDA 206031 on July 20, 2015.

thrombocytopenia <20 x 10^9/L are at risk for potentially fatal complications, including spontaneous intracranial and intrapulmonary hemorrhage.[65]

In 5 out of 8 patients with thrombocytopenia SAEs, the presence of anti-platelet antibodies was confirmed; this is consistent with immune thrombocytopenia. The table below summarizes the anti-platelet antibody data in drisapersen subjects.

Table 24. Anti-platelet antibody data in drisapersen subjects

Subject ID	Anti-platelet antibodies (as reported)
000505	Antibodies against IIb and IIIa glycoproteins positive. Not positive against glycoprotein complex Ia, IIa, Ib and IX. No positive antibodies in serum against the different part of the glycoprotein complex.
000677	Platelet antibody test result: direct anti-GPIIb/IIa slightly positive: 1.2 (normal value less than 1.0); anti-GBIb/IX direct and indirect both negative. Anti-platelet antibodies which showed an increase: direct method (antibody anti-GPIIb/IIIa 5.7, anti-GP1a/IIa 2.8, anti-GPIb/IX 2.2). Indirect antibodies persistently negative.
001025	Slightly positive
001122	Blood circulating anti-platelet antibody result: positive
001176	Marked decrease in number of anti-platelet antibodies: negative.
001202	Subject's anti-platelet antibody (not further specified): positive
002000	Anti-platelet antibodies were reported as positive and broadly reactive, mainly with IIb/IIIa and Ia/IIa.

Source: Table 1, p. 4 BioMarin response to FDA information request. Submitted to NDA 206031 on July 20, 2015.
a thrombocytopenia serious adverse event <50 x 10^9/L, except for Subject 1025, who had a nadir platelet count of 69 x 10^9/L.

Reviewer comment: Anti-platelet antibody testing was not performed in Subjects 687 and 3052. Anti-platelet antibody testing was negative in Subject 1176. Tests for drug-dependent antibodies can be negative in patients with probable drug-induced thrombocytopenia, because assay methods may be insufficiently sensitive to detect some antibodies.[66]

[65] Aster RH. et al. *N Engl J Med* 2007; 357:580-587
[66] George, James N., and Richard H. Aster. "Drug-induced thrombocytopenia: pathogenesis, evaluation, and management." ASH Education Program Book 2009.1 (2009): 153-158.

Table 25. Thrombocytopenia Serious Adverse Events

Subject Age Country	Time from first drisapersen to SAE start (months)	Anti-platelet antibody positive	Nadir platelet count (x 10^9/L)	Description/comment
505 7 France	14	Y	14	Platelet counts were generally normal,[a] including a platelet count of 198 x 10^9/L on March 19, 2015, until a platelet count of 18 x 10^9/L was detected with routine laboratory measurement on April 2, 2013 (when he received his last drisapersen dose). The subject had no symptoms of thrombocytopenia. Drisapersen was stopped. antibodies against thrombocytes were positive (against IIb and IIIb glycoproteins). He received no other treatment for thrombocytopenia was reported. His platelet count returned to normal on June 10, 2013 and remained normal.
677 11 Italy	18	Y	8	Platelet counts were normal, including a platelet count of 138 x 10^9/L on Dec. 7, 2012, until a platelet count of 38 x 10^9/L was detected with routine laboratory measurement on December 20, 2012. Drisapersen was stopped after the dose given on January 4, 2013. On January 8, 2013, he was treated with tranexamic acid, i.v. immunoglobulin, and prednisone. On January 15, the platelet count had decreased to 15 x 10^9/L. He was hospitalized on (b) (6) for a second i.v. immunoglobulin infusion (0.8 g/kg) and tranexamic acid was restarted. Before the second immunoglobulin infusion, anti-thrombocyte antibodies showed an increased response (direct method: AB anti GPIIb / IIIa 5.7, anti GPIa / IIa 2.8, anti GPIb / IX 2.2; while indirect Ab were persistently negative'). The subject had epistaxis on (b) (6). He was discharged on (b) (6) (platelet count was 105 x 10^9/L). On January 22, 2013 he developed diarrhea, hematemesis, and epistaxis. Platelet count was 24 x 10^9/L on Jan. 31, 2013. Prednisone was re-started. On Feb. 6, 2013 his platelet count was 210 x 10^9/L.
687 12 Italy	17	Not tested	5	Platelet counts were normal, including a platelet count of 161 x 10^9/L on Nov. 27, 2012, until a platelet count of 56 x 10^9/L was detected with routine laboratory measurement on December 11, 2012. Last dose of drisapersen was administered on Dec. 11, 2012. Nadir platelet count was 5 x 10^9/L on (b) (6), (b) (6). He was hospitalized and had easy bruising. He was treated with tranexamic acid. His platelet count was normal on Jan. 22, 2013 and Feb. 4, 2013.
1122 10 Chile	26	Y	9	Platelet counts were normal, including a platelet count of 227 x 10^9/L on Sept. 4, 2013, until a platelet count of 9 x 10^9/L was detected with routine laboratory measurement on (b) (6) (date of the last drisapersen dose). He had epistaxis, gingival bleeding, and ecchymoses. He was hospitalized for platelet transfusion, and intravenous immunoglobulin. Anti-platelet antibodies were reported as 'positive.'[67] His platelet count was normal on Oct. 9, 2013 and Jan. 22, 2014.[68]

[67] Table 1, p. 4 BioMarin response to FDA information request. Submitted to NDA 206031 on July 20, 2015.

1176 8 Rep. of Korea	14	N	8	He received drisapersen 6 mg/kg/week in Study 114044 from March 11, 2011 to Feb. 1, 2012. First low platelet count was 78 x 10^9/L on Feb. 7, 2012. On March 21, 2012 (after 7 weeks without drisapersen), his platelet count was 144 x 10^9/L. He restarted drisapersen at the beginning of Study 114349 on March 28, 2012. After 7 weekly injections, his platelet count was 83 x 10^9/L on May 8, 2012. He had petechiae on (b) (6), and drisapersen was discontinued. Platelet count was 17 x 10^9/L, and he was hospitalized for platelet transfusion. He received 2 2-day courses of immunoglobulin therapy (May 17, 2012 and June 7, 2012), as well as steroids. A bone marrow examination performed on May 18, 2012 showed an "adequate number of megakaryocytes with normocellular marrow." Platelet count was normal on June 12, 2012 and remained normal in July 2012. *Reviewer comment: The onset of thrombocytopenia was more gradual, and anti-platelet antibody testing was negative. This patient's thrombocytopenia happened to coincide with an 8 week break from drisapersen at the end of Study 114044, which likely affected the course of his thrombocytopenia.. In this reviewer's opinion, this case is related to drisapersen. He had thrombocytopenia in Study 114044, improved while off of drisapersen treatment for 8 weeks after the end of Study 114044 (positive dechallenge), and had recurrence of thrombocytopenia after restarting drisapersen in extension study 114349.*
1202 7 Taiwan	18	Y	3	Platelet counts were generally normal,[b] including a platelet count of 132 x 10^9/L on Dec. 14, 2015, until a platelet count of 23 x 10^9/L was detected with routine laboratory measurement on Dec. 28, 2013 (when he received his last drisapersen dose). On January 2, 2013 he had bruising and petechiae. He was hospitalized on (b) (6), when his platelet count was 3 x 10^9/L. He was treated with platelet transfusion intravenous immunoglobulin, and prednisolone. On January 12, 2013, his anti-platelet antibodies were reported as 'positive.' By January 18, 2013, platelet count was normal and remained normal at follow-ups in Feb., May, and Nov. 2013.
2000 10 Belgium	29	Y	35	Platelet counts were normal, until he had a low platelet count of 85 x 10^9/L on Dec. 12, 2012. Treatment with drisapersen was interrupted for 1 week and treatment was re-started as the platelet count recovered. On Feb. 14, 2013, his platelet count dropped to 35 x 10^9/L. The subject was withdrawn from the study. The subject did not have symptoms. Anti-platelet antibody tests were positive, mainly reactive with gp IIb/IIIa and gp Ia/IIa. Platelet counts were normal on March 27, 2013 and April 3, 2013.
3052 7 Turkey	10	Not tested	26	Platelet counts were normal, until they decreased gradually: 129 x 10^9/L on April 3, 2013, 104 x 10^9/L on April 17, 2013, 71 x 10^9/L on April 30, 2013 (date of last drisapersen), and 26 x 10^9/L on May 8, 2013. He was hospitalized and treated with intravenous immunoglobulin. His platelet count improved to 171 x10^9/L on May 15, 2013.

[68] Dataset ADLB. Submitted to NDA 206031 on April 27, 2015.

All thrombocytopenia SAEs occurred in extension study DMD114349 while receiving drisapersen 6 mg/kg/week.
Source: Narratives, patient profiles, Sponsor IR responses, and dataset PLTTHR submitted to NDA 206031 on August 20, 2015.
[a] Subject 505 had 2 platelet counts of 128 x 10^9/L on 12/24/2012 and 1/7/2013. (LLN = 130 x 10^9/L)
[b] Subject 1202 had 1 platelet count of 121 x 10^9/L on 6/29/2012.(LLN = 130 x 10^9/L)

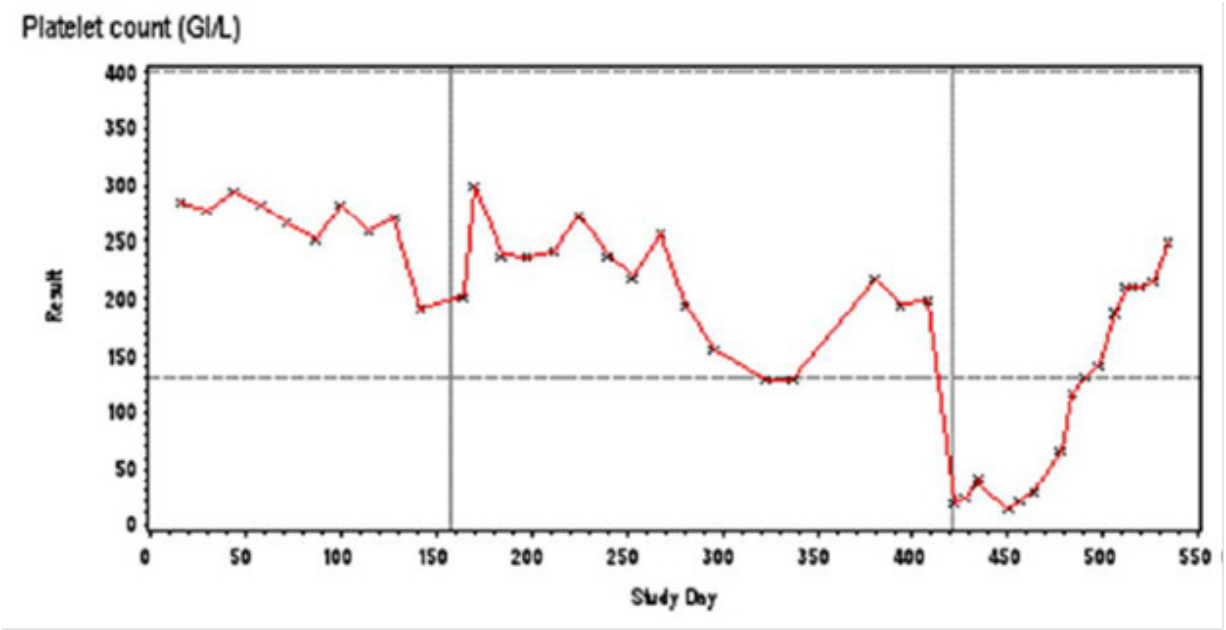
Systematic assessments of anti-platelet antibodies were included in neither the placebo-controlled studies[69] nor the main open-label extension study.[70-71] Other cases of immune thrombocytopenia may have occurred but may not have been detected.

Cases of immune thrombocytopenia with drisapersen were not reported until the open-label extension studies. The reason for this time course for immune thrombocytopenia with drisapersen is unclear. There are no known factors that increase the risk of thrombocytopenia in certain patient subgroups.

The onset of severe immune thrombocytopenia with drisapersen is frequently precipitous and unpredictable. The figures below show the platelet counts by study day for Study 114349 Subjects 505 and 1122, both of whom had treatment-emergent anti-platelet antibodies and a nadir platelet count <20 x 10^9/L. Prior to developing thrombocytopenia, both of these subjects had consistently normal platelet counts, including a normal platelet count within 2 weeks of having a platelet count <20 x 10^9/L.

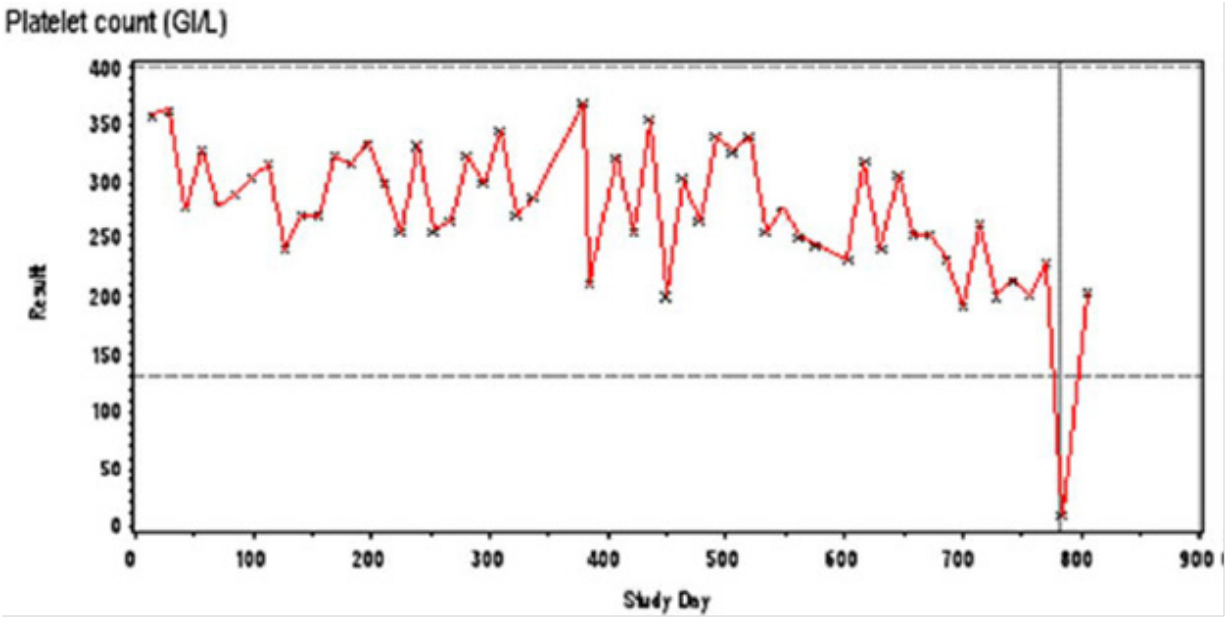
[69] DMD114044, DMD114117, and DMD114876
[70] DMD114349
[71] In the ongoing open-label extension studies DMD115501 (N=21) and DMD114673 (N=12), study protocols were amended to include analysis of clinical samples for any subject who has a confirmed platelet count below 75 x 10^9/L
at a specialist center for analysis of anti-platelet antibodies and platelet function.
At the time of the 120-day safety update report, 1 subject (Study 114673 Subject 105 with nadir platelet count 47 x 10^9/L) received specialist center analysis for antiplatelet antibodies. This subject did not have evidence of antiplatelet antibodies, and the etiology of thrombocytopenia in this subject is unclear.

Figure 3. Subject 505: Platelet counts



Source: Sponsor Figure 12. Summary of Clinical Safety p. 147.

Figure 4. Subject 1122: Platelet counts



Source: Sponsor Figure 15. Summary of Clinical Safety p. 150.

None of the 8 drisapersen subjects who had a thrombocytopenia SAE was rechallenged with drisapersen.[72] According to a review on drug-induced immune thrombocytopenia by Aster:[73] "Once established, drug sensitivity probably persists indefinitely. Therefore, patients should be advised to avoid permanently the medication thought to be the cause of thrombocytopenia."

The Division of Neurology Products consulted the Division of Hematology Products regarding thrombocytopenia with drisapersen.[74] They had the following recommendations:

- Due to the potential increased risk of bleeding in patients with DMD due to abnormally functioning platelets, monitoring and dose adjustment as per protocol DMD114044 should be incorporated into product labeling to limit potential major bleeding and severe thrombocytopenia. Rates of thrombocytopenia and bleeding in clinical practice may differ from the rates seen in clinical studies.

- Drisapersen should not be restarted in patients with thrombocytopenia that recovered after drisapersen discontinuation unless the benefit of therapy outweighs the risk of thrombocytopenia and potential bleeding.

Reviewer comment: This agrees with the recommendations provided by the Division of Hematology Products. Platelet counts were measured every two weeks in clinical studies; this frequency of platelet monitoring will be necessary in the postmarketing setting.
Patients will need to be educated about the signs and symptoms of bleeding related to thrombocytopenia, in order to facilitate prompt diagnosis and treatment.

When considering the use of antiplatelet (e.g., aspirin, adenosine diphosphate receptor inhibitors), thrombolytic (e.g., tissue plasminogen activator, streptokinase), or anticoagulant drugs (e.g., heparin, warfarin) concomitantly with drisapersen, I recommend consideration of the risk of potential bleeding from thrombocytopenia. Patients taking these drugs were excluded from clinical studies.

8.5.2. **Renal Toxicity**

Renal toxicity: Adverse events

The kidney is a target organ for drisapersen with drug accumulating in the proximal tubule.[75] Oligonucleotides are filtered at the glomerulus and reabsorbed by proximal tubule

[72] P. 6. BioMarin response to FDA information request. Submitted to NDA 206031 on July 20, 2015.
[73] Aster RH. et al. N Engl J Med 2007; 357:580-587
[74] 8/12/2015

epithelium.[76] In nonclinical studies, dose-related accumulation of drisapersen occurred in the renal tubule epithelial cells. In placebo-controlled studies in humans, 60.9% of drisapersen 6 mg/kg/week subjects had a renal toxicity adverse event, compared to 33.7% of placebo subjects (see table below).[77]

Table 26. Summary of on-treatment renal toxicity adverse events by preferred term (placebo-controlled studies)

Adverse event System organ class Preferred term	Placebo N=95 n (%)	Drisapersen 6mg/kg/wk N=161 n (%)
Any renal abnormality	32 (33.7)	98 (60.9)
Proteinuria	16 (16.8)	47 (29.2)
Haematuria	5 (5.3)	24 (14.9)
Protein urine present	6 (6.3)	20 (12.4)
Cystatin C increased	4 (4.2)	17 (10.6)
Red blood cells urine positive	4 (4.2)	15 (9.3)
Urine protein/creatinine ratio increased	4 (4.2)	14 (8.7)
Red blood cells urine	5 (5.3)	13 (8.1)
Protein urine	0	8 (5.0)
Urine analysis abnormal	0	3 (1.9)
Urinary sediment present	1 (1.1)	2 (1.2)
Nephropathy toxic	0	2 (1.2)
Albuminuria	0	2 (1.2)
Urine protein/creatinine ratio	0	2 (1.2)
Cystatin C	1 (1.1)	1 (0.6)
White blood cells urine positive	0	1 (0.6)
Protein total increased	0	1 (0.6)
Red blood cell count increased	0	1 (0.6)
Creatinine renal clearance decreased	0	1 (0.6)
Urine leukocyte esterase positive	0	1 (0.6)
Urine protein/creatinine ratio abnormal	0	1 (0.6)
White blood cell count	0	1 (0.6)
Chromaturia	2 (2.1)	1 (0.6)
Renal impairment	1 (1.1)	1 (0.6)
Glomerulonephritis	0	1 (0.6)
Myoglobinuria	0	1 (0.6)
Red blood cell abnormality	0	1 (0.6)
Glycosuria	1 (1.1)	0
Nephrolithiasis	1 (1.1)	0
Urine abnormality	1 (1.1)	0

Source: Sponsor Table 54 on Summary of Clinical Safety p. 113.
Table includes data from studies DMD114117, DMD114044, and DMD114876.

Reviewer comment: Analyses were performed to combine the frequencies of split terms related to renal toxicity.[78] In placebo-controlled studies, proteinuria[79] occurred in 70 of 161 (43.5%)

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[75] P. 122. Summary of Clinical Safety; Section 2.7.4 of the April 27, 2015 submission to NDA 206031.
[76] P. 22 Nonclinical Overview. Submitted to NDA 206031 on 10/10/2014.
[77] In placebo-controlled studies, 70.6% and 11.8% of drisapersen subjects had a renal toxicity adverse event in the 6 mg/kg/week intermittent and 3 mg/kg/week dose groups, respectively. These results are limited by small sample sizes (17 subjects in each group). (ISS Table 11.63.1 on ISS p. 2589-2590)
[78] Table 1. ISS addendum submitted to NDA 206031 on 09/25/2015.

drisapersen 6 mg/kg/week subjects, compared to 22 of 95 (23.2%) placebo subjects. Hematuria[80] occurred in 26 of 161 (16.1%) drisapersen 6 mg/kg/week subjects, compared to 10 of 95 (10.5%) placebo subjects.

In repeat-dose studies, 71.5% of drisapersen 6 mg/kg/week subjects had a renal toxicity adverse event (see table below).

[79] Adverse events with PTs Proteinuria, Protein urine present, and Protein urine were combined. Subjects with adverse events coded to more than 1 of the 3 terms and were counted once.
[80] Hematuria-- Subjects had an adverse event coded to at least one of these Preferred Terms: Red blood cells urine positive, or Red blood cells urine

Table 27. Summary of on-treatment renal toxicity adverse events by preferred term (repeat dose studies)

Adverse event preferred term	Placebo N=95 n (%)	Drisapersen 3mg/kg/wk N=17 n (%)	Drisapersen 6mg/kg/wk N=267 n (%)	Drisapersen 6mg/kg intermittent[a] N=38 n (%)	Drisapersen all regimens[b] N=285 n (%)
Any renal abnormality AE	**32 (33.7)**	**2 (11.8)**	**191 (71.5)**	**29 (76.3)**	**194 (68.1)**
Proteinuria	16 (16.8)	1 (5.9)	115 (43.1)	12 (31.6)	118 (41.4)
Protein urine present	6 (6.3)	0	42 (15.7)	7 (18.4)	47 (16.5)
Haematuria	5 (5.3)	0	43 (16.1)	4 (10.5)	44 (15.4)
Cystatin C increased	4 (4.2)	0	33 (12.4)	11 (28.9)	40 (14.0)
Red blood cells urine positive	4 (4.2)	0	36 (13.5)	3 (7.9)	39 (13.7)
Urine protein/creatinine ratio increased	4 (4.2)	0	30 (11.2)	7 (18.4)	36 (12.6)
Red blood cells urine	5 (5.3)	1 (5.9)	24 (9.0)	3 (7.9)	27 (9.5)
Albuminuria	0	0	9 (3.4)	12 (31.6)	16 (5.6)
Protein urine	0	0	13 (4.9)	2 (5.3)	15 (5.3)
Alpha 1 microglobulin urine increased	0	0	11 (4.1)	7 (18.4)	11 (3.9)
White blood cells urine positive	0	0	5 (1.9)	3 (7.9)	8 (2.8)
Urinary sediment present	1 (1.1)	0	6 (2.2)	0	6 (2.1)
Urinary sediment abnormal	0	0	5 (1.9)	4 (10.5)	5 (1.8)
Red blood cell count increased	0	0	4 (1.5)	1 (2.6)	5 (1.8)
Nephropathy toxic	0	0	5 (1.9)	0	5 (1.8)
Urinary casts	0	0	5 (1.9)	0	5 (1.8)
Urine analysis abnormal	0	0	4 (1.5)	1 (2.6)	5 (1.8)
Albumin urine present	0	0	3 (1.1)	0	3 (1.1)
Renal impairment	1 (1.1)	0	3 (1.1)	0	3 (1.1)
Chromaturia	2 (2.1)	1 (5.9)	1 (0.4)	0	2 (0.7)
Myoglobinuria	0	0	2 (0.7)	0	2 (0.7)
Blood urine present	0	0	2 (0.7)	0	2 (0.7)
Creatinine renal clearance decreased	0	0	2 (0.7)	0	2 (0.7)
Protein total increased	0	0	1 (0.4)	1 (2.6)	2 (0.7)
Urine protein/creatinine ratio	0	0	2 (0.7)	0	2 (0.7)
Urine /protein/creatinine ratio abnormal	0	0	2 (0.7)	0	2 (0.7)
White blood cells urine	0	0	0	2 (5.3)	2 (0.7)
Cystatin C	1 (1.1)	0	1 (0.4)	0	1 (0.4)
Glycosuria	1 (1.1)	0	1 (0.4)	0	1 (0.4)
Glomerulonephritis	0	0	1 (0.4)	0	1 (0.4)
Haemoglobinuria	0	0	1 (0.4)	0	1 (0.4)
Leukocyturia	0	0	1 (0.4)	0	1 (0.4)
Albumin globulin ratio increased	0	0	1 (0.4)	0	1 (0.4)
Albumin urine	0	0	1 (0.4)	0	1 (0.4)
Alpha 1 microglobulin	0	0	0	1 (2.6)	1 (0.4)
Alpha-2 macroglobulin increased [c]	0	0	1 (0.4)	0	1 (0.4)
Creatine urine increased	0	0	1 (0.4)	0	1 (0.4)
Light chain analysis increased	0	0	0	1 (2.6)	1 (0.4)
Protein albumin ratio increased	0	0	0	1 (2.6)	1 (0.4)
Urine leukocyte esterase positive	0	0	1 (0.4)	0	1 (0.4)
White blood cell count	0	0	1 (0.4)	0	1 (0.4)
pH urine increased	0	0	1 (0.4)	0	1 (0.4)
Red blood cell abnormality	0	0	1 (0.4)	0	1 (0.4)
Nephrolithiasis	1 (1.1)	0	0	0	0
Urine abnormality	1 (1.1)	0	0	0	0

Source: Sponsor Table 53 on Summary of Clinical Safety p. 111.

[a] intermittent includes subjects dosed with 9 doses in a 10-week cycle

[b] Subjects treated with more than one drisapersen regimen are only counted once in this group.

[c] The verbatim text for this preferred term was 'periods of elevated alpha 1 microglobuline 45.2 mg/L'.

Reviewer comment: This adverse event appears to be miscoded and would underestimate the occurrence of the event. If the alpha 1 microglobulin measurement is from the serum, the measurements are mildly elevated. The normal range for serum alpha 1 microglobulin has been reported as 20-42 mg/L (Weber MH. Klin Wochenschr. 1985 Aug 1;63(15):711-7.)

Table includes data from studies DMD114117, DMD114044, DMD114876, DMD114349, PRO051-02, and DMD114673.

Reviewer comment: In analyses of repeat dose studies performed to combine the frequencies of split terms,[81] proteinuria[82] occurred in 161 of 267 (60.3%) of drisapersen 60 mg/kg/week subjects. Hematuria[83] occurred in 53 of 267 (19.9%) drisapersen 6 mg/kg/week subjects.

In placebo-controlled studies, 2 of 195 (1%) drisapersen-treated subjects had a renal SAE, compared to 0 of 95 placebo-treated subjects:

- **PT Glomerulonephritis**

  DMD114044 Subject 527,[84] a 10 year old boy from France, had no history of kidney disease or kidney disease risk factors prior to study entry. He started drisapersen 6 mg/kg/week on April 6, 2011. Baseline spot urine protein (March 15, 2011) was 0.06 g/L. On September 21, 2011, spot urine protein rose to 0.5 g/L. Spot urine protein was 1.1 g/L on October 5, 2011 and 1.6 g/L on October 21, 2011.

  The study's monitoring criteria required a 24-hour urinalysis after 2 consecutive urine protein ≥ 0.2 g/L on 2 consecutive weekly samples). However, this subject did not have a 24-hour urinalysis until one month after the first spot urine protein ≥ 0.2 g/L .

  On October 26, 2015, 5.8 g of protein was measured in a 24 hour urine collection. (Nephrotic range proteinuria is defined as 1 g/day in children.) The last drisapersen dose was administered on (b) (6).

  After cessation of drisapersen treatment, spot urine protein measurements increased to 8.05 and 8.96 g/L on November 2 and 9, 2011, respectively. On (b) (6), (26 days after last drisapersen dose), the subject was hospitalized with left sided back pain, and developed tachycardia and tachypnea. Bilateral pulmonary emboli were diagnosed (left pulmonary artery and right middle lobe). On (b) (6) CT scan showed thrombosis of the inferior vena cava and right renal vein with infarction of the right kidney.[85] Kidney biopsy obtained on (b) (6), showed type 1 grade 2 (moderate) membranous glomerulonephritis.

  The subject was treated with anticoagulation. On December 12, 2011 spot urine protein was 1.1 g/L. Doppler ultrasound in June 2012 showed no evidence of thrombus the

[81] Table 1. ISS addendum submitted to NDA 206031 on 09/25/2015.
[82] Proteinuria -- Subjects had an adverse event coded to at least one of these Preferred Terms: Proteinuria, Protein urine present, Protein urine, or Albuminuria.
[83] Hematuria-- Subjects had an adverse event coded to at least one of these Preferred Terms: Red blood cells urine positive, or Red blood cells urine

[85] Safety report submitted to IND 067476 on December 23, 2011.

renal vein or inferior vena cava. His proteinuria eventually improved to 0.11 g /day on 24 hour urinalysis. (Follow-up date June 25, 2102; test date not reported.)

Serum cystatin C was 0.7mg/L at screening (normal range 0.6 - 0.8 mg/L). At study withdrawal (12/12/2011), serum cystatin C was 1.0 mg/L. No serum electrolyte abnormalities were reported.

This event is likely related to drisapersen. Membranous glomerulonephritis is a rare disease in children.[86-87] Membranous glomerulonephritis is related to immune deposits in the kidney. It is unclear whether anti-drisapersen antibodies contributed to this case. Subject's kidney biopsy sample was not tested for anti-drisapersen antibodies, and conclusive plasma anti-drisapersen antibody testing was not performed in this subject.

- **PT Haematuria** – DMD114117 Subject 3000:[88]

  Hours after having a protocol-required muscle biopsy while under general anesthesia, this 7 year old subject developed frank hematuria. Urine myoglobin was 182 mg/L (normal = ≤0.1 mg/L). Electrolytes, renal function tests, coagulation tests, and renal ultrasound were normal. The event resolved after 6 days.

  Reviewer comment: This event is unrelated to drisapersen. The subject had anesthesia-associated rhabdomyolysis, which has been reported in children with congenital muscle disease, including DMD.[89]

In extension studies there were 2 renal SAEs in drisapersen-treated subjects:

- **PT Proteinuria** – DMD144044 / DMD114349 Subject 1124:[90]

  This 8 year old boy received all planned drisapersen doses in Study 114044 (starting on August 10, 2011), in which his peak 24 hour urinalysis measurement was 0.2 g/24 hours.[91] He was first dosed in Study DMD114349 on August 8, 2012. His spot urine

[86] Eddy AA, et al. Nephrotic syndrome in childhood. Lancet 2003; 362: 629–39.
[87] Nephrotic syndrome in children: Prediction of histopathology from clinical and laboratory characteristics at time of diagnosis. International Study of Kidney Disease in Children. Kidney International, Vol. 13 (1978), pp. 159 —165.
[88] Narrative on p. 3817 Integrated Summary of Safety (ISS); Section 5.3.5.3 of the April 27, 2015 submission to NDA 206031.
[89] Pedrozzi, NE. Rhabdomyolysis and anesthesia: a report of two cases and review of the literature. *Pediatric neurology.* 15.3 (1996): 254-257.
[90] Narrative on p. 4349 Integrated Summary of Safety (ISS); Section 5.3.5.3 of the April 27, 2015 submission to NDA 206031.
[91] The treatment stopping criterion for protein in a 24 hour urine sample was >0.3 g/day and double the baseline value, according to the document titled "January 6, 2012 Discussion"; Section 1.11.4 of the 1/11/2012 submission to IND 105284.

protein on 8/8/2012 was 0.2 g/L. Two weeks later on 8/22/2012, his spot urine protein was 5.2 g/L. He continued to receive drisapersen, on August 29, 2012 and September 5, 2012. On September 5, 2012, 24 hour urine protein was 11.0 g/day. Drisapersen treatment was discontinued. Urine protein decreased after discontinuation of drisapersen (see table below).

Table 28. Subject 1124: 24-hour protein measurements

Date of measurement	24-hour urine protein measurement (g/day)
9/5/2012	11.0
9/11/2012	6.8
9/19/2012	4.5
10/2/2012	2.8
10/23/2012	0.3
11/13/2012	0.1
5/14/2013	0.1

Source: Dataset ADLB2349[92]

There was no frank edema or hypoalbuminemia reported.

Reviewer comment: In the opinion of this reviewer, this case is likely related to drisapersen.

- **PT Renal impairment** -- DMD144044 / DMD114349 Subject 1002:[93]

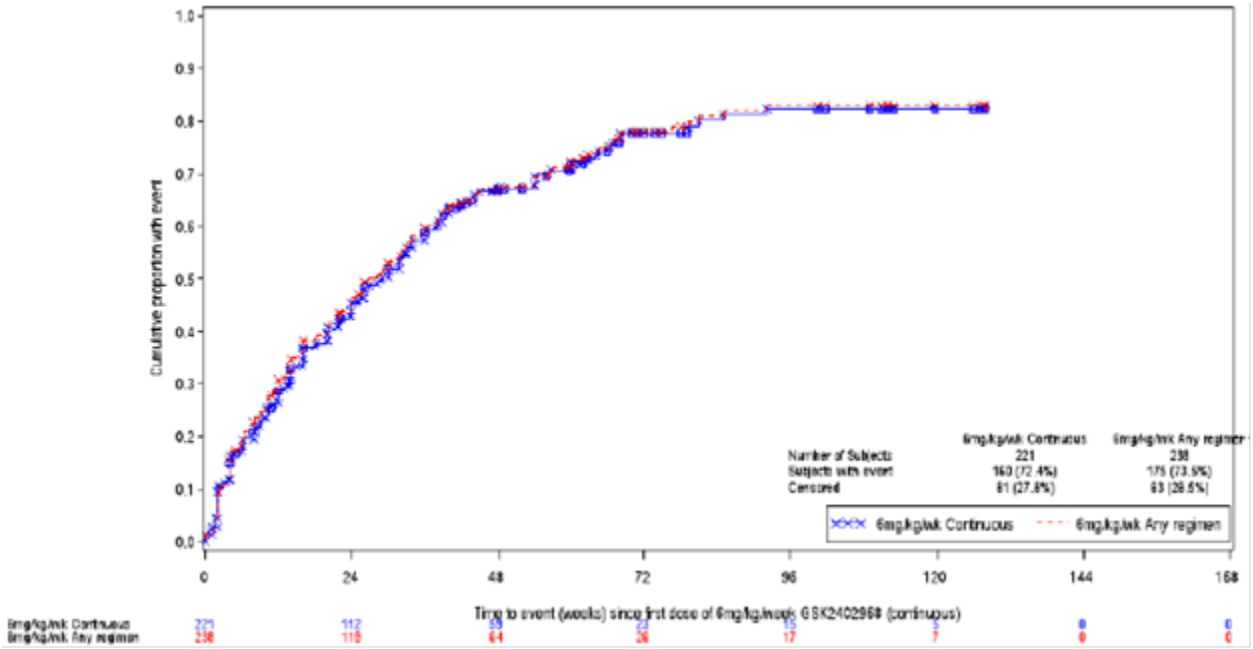
  Twenty three months after his first drisapersen dose on Study 114044, this 9 year old boy presented with acute renal failure (increased BUN and creatinine) in the setting of a viral infection, diarrhea, and volume depletion. He received fluid and electrolyte replacement. The event was resolved after 8 days.

  Reviewer comment: This event is related to volume depletion in the setting of a viral infection and diarrhea and is unrelated to drisapersen.

The figure below shows the time to first renal toxicity in drisapersen Study DMD114349 subjects.

[92] Section 5.3.5.2 of the 7/29/15 submission to NDA 206031.
[93] Narrative on p. 3828 Integrated Summary of Safety (ISS); Section 5.3.5.3 of the April 27, 2015 submission to NDA 206031.

Figure 5. Cumulative distribution of time to first renal toxicity adverse event for subjects receiving drisapersen 6 mg/kg/week in DMD114349, by treatment in the parent study (DMD114349 and parent studies – long-term safety)



Source: SCS Figure 7 p. 119.
Figure includes data from studies DMD114117, DMD114044, and DMD114349.

In all repeat dose studies, 36 of 1183 (3.2%) renal toxicity adverse events were unresolved at the end of the study. In the drisapersen 6 mg/kg/week group, events that were unresolved were proteinuria (13 events), cystatin C increased (14 events), protein urine present (2 events), urinary sediment present (2 events), urinary casts (1 event) and glomerulonephritis (1 event). The median duration of renal adverse events in drisapersen 6 mg/kg/week subjects was 41 days.

Renal toxicity: Laboratory data

Urinalysis results for the ambulant placebo-controlled studies showed mean increases in urine protein that were greater with drisapersen 6 mg/kg/week than with placebo. In placebo-controlled studies, mean changes from baseline for drisapersen 6 mg/kg/week, were 47 mg/L at Week 12, 70 mg/L at Week 24, 72 mg/L at Week 36, and 64 mg/L at Week 48 compared with mean changes of 3, 5, 8, and 6 mg/L, respectively for placebo. Thirty percent of drisapersen 6 mg/kg/week subjects had a high (≥0.15 g/ day) 24 hour urine protein, compared to 4% of placebo subjects.[94]

[94] Table 10.2 on p. 149 of the ISS addendum submitted on 7/20/2015 to NDA 206031.

There were no clinically significant changes in urine red blood cells, white blood cells or casts in drisapersen subjects, compared to placebo.

Creatinine as a marker of renal function has limited value in Duchenne muscular dystrophy (DMD), because of reduced muscle mass. Cystatin C has been evaluated as a biomarker for monitoring renal function in DMD,[95] and it was measured in drisapersen clinical studies. The range of normal values for cystatin C is 0.6-0.8 mg/L. In placebo-controlled studies, 58% of drisapersen 6 mg/kg/week subjects went from a normal cystatin C at baseline to a high value post-treatment, compared to 27% of placebo subjects.[96] In placebo-controlled studies, the median maximum post-baseline cystatin C level in drisapersen 6 mg/kg/week subjects was 0.9 mg/L (interquartile range 0.8-1.0), compared to 0.8 mg/L for placebo (interquartile range 0.7-0.9) (see table below).

Table 29. Summary of maximum post-baseline cystatin C (mg/L). Placebo-controlled studies.

		Drisapersen			
	Placebo (N=95)	3mg/kg/week (N=17)	6mg/kg/week (N=161)	6mg/kg Intermittent (N=17)	All Regimens (N=195)
n	95	17	161	17	195
Mean (SD)	0.81 (0.108)	0.83 (0.110)	0.94 (0.145)	0.94 (0.154)	0.93 (0.146)
Median	0.80	0.80	0.90	0.90	0.90
Q1, Q3	0.7, 0.9	0.7, 0.9	0.8, 1.0	0.9, 1.0	0.8, 1.0
Min, Max	0.6, 1.1	0.7, 1.0	0.7, 1.5	0.7, 1.3	0.7, 1.5

Source: P. 11 Section 1.11.4 of the 7/29/2015 submission to NDA 206031

Reviewer comment: While treatment-emergent increases in cystatin C were more frequent in drisapersen subjects, the changes were small and not sustained. The interquartile ranges for maximum post-baseline cystatin C were overlapping for the drisapersen 6 mg/kg/week and placebo groups. The highest cystatin C measurement of 1.5 mg/L (in drisapersen 6 mg/kg/week subject 235) was not treatment-emergent. Subject 235's baseline cystatin C was 1.2 mg/L for unclear reasons.

Placebo-controlled studies did not indicate evidence of blood electrolyte abnormalities, which can occur with renal tubular dysfunction (e.g., Fanconi syndrome). (See Section 8.4.6 Laboratory Findings)

[95] Violett L. Utility of Cystatin C to monitor renal function in Duchenne muscular dystrophy. *Muscle Nerve*. 2009 September ; 40(3): 438–442. doi:10.1002/mus.21420.
[96] P. 96 of the ISS addendum in Section 5.3.5.2 of the 7/20/2015 submission to NDA 206031.

Renal toxicity: Reviewer discussion and recommendations

In the submitted product label, the Sponsor proposes renal monitoring and stopping criteria as follows: "Monitor for urine protein by urine dipstick analysis once a month during [TRADENAME] treatment. Patients with a dipstick of 3+ for protein should undergo a 24 hour urine collection. Suspend [TRADENAME] treatment when urine protein is >1 gram per 24 hours. Treatment may be resumed when urine protein is ≤ 1 gram per 24 hours and based on individual risk-benefit assessment. Discontinue treatment if patient develops glomerulonephritis."[97]

In the opinion of this reviewer, Sponsor's proposed method (urine dipstick testing) and frequency of renal monitoring, as well as the proposed renal criterion for stopping drisapersen treatment, are not acceptable.

In repeat dose studies of drisapersen, 2 of 285 (0.7%)[98] of subjects had a renal toxicity SAE that was related to drisapersen treatment. With each of these SAEs, there was a rapid progression of proteinuria severity, with urine spot protein increasing at least 3 fold within a month. In the membranous glomerulonephritis SAE (Subject 527), potentially fatal thromboses with bilateral pulmonary emboli ensued. This subject's proteinuria and clinical condition worsened for about 1 month after drisapersen was discontinued.

In the postmarketing setting, baseline renal testing and frequent renal monitoring will be necessary, especially because of the potential for: a) rapid progression of renal toxicity; b) a time period of worsening renal toxicity after drisapersen treatment discontinuation; and c) serious and potentially fatal consequences of renal toxicity.

In clinical studies, subjects had scheduled quantitative urine protein testing every 2 weeks. Drisapersen treatment stopping criteria included:[99]

- Urinary protein concentration ≥0.2 g/L and <0.45g/L on two consecutive weekly samples;

(If urinary protein concentration was ≥0.45 g/L on urinalysis, study drug was stopped and the urinary protein analysis was repeated. If the repeat urinary protein value was ≥0.2 g/L, investigators were advised to continue to hold the study drug and perform a 24 hour urine test. If the repeat urinary protein value was <0.2 g/L, the study drug could be restarted.)

- Protein/creatinine ratio in the morning sample is >0.5 on two consecutive samples;
- Serum concentration of cystatin C is above the normal range and 50%above the baseline value.
- If the results of the 24 hour urine test triggered by any of the above do not meet criteria defined below, study drug may be restarted

[97] Monitoring to Assess Safety Section 2.2. Sponsor proposed product label. Submitted to NDA 206031 on 4/27/2015.
[98] Subject 527 (PT Glomerulonephritis) and Subject 1124 (PT Proteinuria).
[99] Latest iteration of renal treatment stopping criteria (circa April – June 2012). P. 219 of the Summary of Clinical Safety.

- Proteinuria in 24-hour urine sample is >300 mg/day and double the baseline value.

The clinical study stopping and follow-up parameters were reviewed and agreed upon by (b) (4) . (b) (4) served on the GlaxoSmithKline Independent Data Monitoring Committee (IDMC), which periodically reviewed unblinded safety data from placebo-controlled studies.

The sponsor's proposal to use a urine dipstick of 3+ for protein as a screening test for significant proteinuria is inadequate. Urine dipstick testing was not used in clinical studies. In a published study of children known to have nephrotic syndrome, urine dipstick of 3+ or 4+ had only a 70% sensitivity to detect a 24 hour urine protein excretion of >1g.[100]

Reviewer conclusion: In the postmarketing setting, baseline renal testing and renal monitoring every 2 weeks will necessary. Criteria for discontinuing drisapersen treatment based on renal testing should be similar to stopping criteria used in clinical studies.

8.5.3. Injection Site Reactions

In repeat dose studies, 210 of 267 (78.7%) drisapersen 6 mg/kg/week subjects reported at least 1 injection site reaction (see table below).

Table 30. Summary of injection site reactions (repeat dose studies)

Adverse event	Placebo N=95 n (%)	Drisapersen 3mg/kg/wk N=17 n (%)	Drisapersen 6mg/kg/wk N=267 n (%)	Drisapersen 6mg/kg intermittent[a] N=38 n (%)	Drisapersen all regimens[b] N=285 n (%)
Any injection site reaction	21 (22.1)	11 (64.7)	210 (78.7)	31 (81.6)	224 (78.6)
Any injection site reaction SAE	0	0	2 (0.7)	0	2 (0.7)
Any severe injection site reaction	0	0	9 (3.4)	0	10 (3.5)

Source: Sponsor Table 47. Summary of Clinical Safety
Includes data from studies DMD114117, DMD114044, DMD114876, DMD114349, PRO051-02, and DMD114673.

Two drisapersen subjects (both receiving 6 mg/kg/week) had injection site reaction SAEs:

- DMD114349 Subject 511, a 9 year old subject from France, started drisapersen in March 2011. On (b) (6), he received his dose and developed severe injection site edema on the back of his upper arm. Ultrasound showed edema and infiltration of subcutaneous tissues. He was hospitalized and treated with paracetamol. The event resolved after 7 days. Treatment with drisapersen was discontinued.

[100] Abitbol, Carolyn, et al. "Quantitation of proteinuria with urinary protein/creatinine ratios and random testing with dipsticks in nephrotic children." The Journal of pediatrics 116.2 (1990): 243-247.

- DMD114349 Subject 126, a 6 year old subject from Poland, started drisapersen in July 2011. On (b) (6), he developed severe injection site edema in his upper arm. The next day he developed fever and was hospitalized and treated with prednisone. The event resolved after 2 days. He continued drisapersen treatment.

Ten of 285 (3.5%) drisapersen subjects reported severe injection site reactions, including injection site atrophy, injection site pain, injection site induration, injection site discoloration, and injection site edema.

The table below summarizes injection site reactions in repeat dose studies by MedDRA Preferred Term. The most common injection site reaction Preferred Terms were Injection site erythema and Injection site discolouration, reported in 52.1% and 47.2% of drisapersen 6 mg/kg/week subjects, respectively. Other injection site reaction PTs reported in at least 10% of drisapersen 6 mg/kg/week subjects included: Injection site induration (29.6%), Injection site pain (19.5%), Injection site reaction (18.4%), Injection site pruritus (16.9%), Injection site bruising (13.1%), Injection site atrophy (12.0%), Injection site haematoma (12.0%), and Injection site swelling (10.1%).

Table 31. Summary of on-treatment injection site reactions by preferred terms (repeat dose studies)

Adverse event preferred term	Placebo N=95 n (%)	Drisapersen 3mg/kg/wk N=17 n (%)	Drisapersen 6mg/kg/wk N=267 n (%)	Drisapersen 6mg/kg intermittent[a] N=38 n (%)	Drisapersen all regimens[b] N=285 n (%)
Any on-treatment injection site reaction AE	21 (22.1)	11 (64.7)	210 (78.7)	31 (81.6)	224 (78.6)
Injection site erythema	8 (8.4)	10 (58.8)	139 (52.1)	16 (42.1)	157 (55.1)
Injection site discolouration	5 (5.3)	5 (29.4)	126 (47.2)	18 (47.4)	133 (46.7)
Injection site induration	1 (1.1)	0	79 (29.6)	14 (36.8)	81 (28.4)
Injection site pain	5 (5.3)	0	52 (19.5)	12 (31.6)	58 (20.4)
Injection site pruritus	1 (1.1)	2 (11.8)	45 (16.9)	7 (18.4)	54 (18.9)
Injection site reaction	1 (1.1)	0	49 (18.4)	5 (13.2)	52 (18.2)
Injection site atrophy	0	0	32 (12.0)	10 (26.3)	42 (14.7)
Injection site bruising	9 (9.5)	2 (11.8)	35 (13.1)	3 (7.9)	41 (14.4)
Injection site haematoma	5 (5.3)	0	32 (12.0)	12 (31.6)	39 (13.7)
Injection site swelling	0	1 (5.9)	27 (10.1)	3 (7.9)	31 (10.9)
Injection site inflammation	0	0	13 (4.9)	2 (5.3)	13 (4.6)
Injection site urticaria	0	0	13 (4.9)	1 (2.6)	13 (4.6)
Injection site rash	2 (2.1)	0	10 (3.7)	1 (2.6)	11 (3.9)
Injection site oedema	0	0	11 (4.1)	0	11 (3.9)
Injection site vesicles	0	0	10 (3.7)	1 (2.6)	11 (3.9)
Injection site dryness	0	0	10 (3.7)	1 (2.6)	10 (3.5)
Injection site macule	1 (1.1)	0	7 (2.6)	2 (5.3)	9 (3.2)
Injection site warmth	0	0	7 (2.6)	0	7 (2.5)
Injection site scab	0	0	5 (1.9)	0	5 (1.8)
Injection site haemorrhage	0	0	4 (1.5)	1 (2.6)	4 (1.4)
Fat tissue decreased	0	0	4 (1.5)	0	4 (1.4)
Injection site irritation	0	0	3 (1.1)	1 (2.6)	4 (1.4)
Application site vesicles	0	0	3 (1.1)	0	3 (1.1)
Injection site anaesthesia	0	0	3 (1.1)	0	3 (1.1)
Injection site erosion	0	0	3 (1.1)	0	3 (1.1)
Injection site exfoliation	0	0	3 (1.1)	0	3 (1.1)
Injection site mass	0	0	3 (1.1)	0	3 (1.1)
Injection site nodule	0	0	3 (1.1)	0	3 (1.1)
Injection site ulcer	0	0	0	3 (7.9)	3 (1.1)
Injection site extravasation	0	0	2 (0.7)	0	2 (0.7)
Injection site hypersensitivity	0	0	2 (0.7)	0	2 (0.7)
Injection site hypertrophy	0	0	2 (0.7)	0	2 (0.7)
Injection site movement impairment	0	0	2 (0.7)	0	2 (0.7)
Injection site plaque	0	0	2 (0.7)	0	2 (0.7)
Infusion site bruising	0	0	1 (0.4)	0	1 (0.4)
Injection site calcification	0	0	0	1 (2.6)	1 (0.4)
Injection site dysaesthesia	0	0	1 (0.4)	0	1 (0.4)
Injection site eczema	0	0	0	1 (2.6)	1 (0.4)
Injection site hyperaesthesia	0	0	1 (0.4)	0	1 (0.4)
Injection site injury	0	0	1 (0.4)	0	1 (0.4)
Injection site paraesthesia	0	0	1 (0.4)	0	1 (0.4)
Injection site scar	0	0	1 (0.4)	0	1 (0.4)
Mass	0	0	1 (0.4)	0	1 (0.4)
Infusion site haematoma	1 (1.1)	0	0	0	0
Injection site papule	1 (1.1)	0	0	0	0
Lipodystrophy acquired	0	0	4 (1.5)	0	4 (1.4)
Pigmentation disorder	1 (1.1)	0	3 (1.1)	0	3 (1.1)
Erythema	0	0	2 (0.7)	1 (2.6)	3 (1.1)
Macule	0	0	1 (0.4)	1 (2.6)	2 (0.7)
Skin hyperpigmentation	0	0	2 (0.7)	0	2 (0.7)
Pain of skin	0	0	1 (0.4)	0	1 (0.4)
Pruritus generalised	0	0	1 (0.4)	0	1 (0.4)
Rash macular	0	0	1 (0.4)	0	1 (0.4)
Skin discolouration	0	0	1 (0.4)	0	1 (0.4)

Adverse event preferred term	Placebo N=95 n (%)	Drisapersen 3mg/kg/wk N=17 n (%)	Drisapersen 6mg/kg/wk N=267 n (%)	Drisapersen 6mg/kg intermittent[a] N=38 n (%)	Drisapersen all regimens[b] N=285 n (%)
Skin fibrosis	0	0	1 (0.4)	0	1 (0.4)
Injection related reaction	0	0	10 (3.7)	1 (2.6)	10 (3.5)
Contusion	1 (1.1)	0	3 (1.1)	0	3 (1.1)
Post procedural complication	0	0	1 (0.4)	0	1 (0.4)
Skin injury	0	0	1 (0.4)	0	1 (0.4)
Hyperaemia	0	0	3 (1.1)	0	3 (1.1)
Haematoma	0	0	2 (0.7)	0	2 (0.7)
Injection site cellulitis	0	0	2 (0.7)	0	2 (0.7)

Source: Sponsor Table 48. Summary of Clinical Safety.
Includes data from studies DMD114117, DMD114044, DMD114876, DMD114349, PRO051-02, and DMD114673.

Analyses were performed to combine the frequencies of split terms for injection site reactions.[101] In placebo-controlled studies, skin discoloration[102] occurred in 58 of 161 (36.0%) drisapersen 6 mg/kg/week subjects, compared to 7 of 95 (7.4%) placebo subjects. Chronic skin damage[103] occurred in 19 of 161 (11.8%) drisapersen 6 mg/kg/week subjects, compared to 1 of 95 (1.1%) placebo subjects. Ulceration[104] occurred in 5 of 161 (3.7%) drisapersen 6 mg/kg/week subjects, compared to 0 of 95 placebo subjects. Injection site hair growth[105] occurred in 10 of 161 (6.2%) drisapersen 6 mg/kg/week subjects, compared to 0 of 95 placebo subjects.

In repeat dose studies, skin discoloration[106] occurred in 130 of 267 (48.7%) drisapersen 6 mg/kg/week subjects. Chronic skin damage[107] occurred in 49 of 267 (18.4%) drisapersen 6 mg/kg/week subjects. Ulceration[108] occurred in 19 of 267 (7.1%) drisapersen 6 mg/kg/week

[101] Table 2. ISS addendum submitted to NDA 206031 on 09/25/2015.
[102] Skin discoloration -- Subjects had an injection site reaction adverse event coded to at least one of these Preferred Terms: Injection site discoloration, Pigmentation disorder, Skin hyperpigmentation, or Skin discoloration.
[103] Chronic skin damage -- Subjects had an injection site reaction adverse event coded to at least one of these Preferred Terms: Atrophy, Fat tissue decreased, Injection site nodule, Hypertrophy, Plaque, Calcification, Scar, Mass, Acquired lipodystrophy, or Skin fibrosis.
[104] Ulceration -- Subjects had an injection site reaction adverse event coded to at least one of these Preferred Terms: Injection site vesicles, Application site vesicles, Injection site erosion, Injection site ulcer, or Injection site scab
[105] Hair growth -- Subjects had an injection site reaction adverse event coded to at least one of these Preferred Terms: Hair growth, Hypertrichosis, or Hirsutism at injection site.
[106] Skin discoloration -- Subjects had an injection site reaction adverse event coded to at least one of these Preferred Terms: Injection site discoloration, Pigmentation disorder, Skin hyperpigmentation, or Skin discoloration.
[107] Chronic skin damage -- Subjects had an injection site reaction adverse event coded to at least one of these Preferred Terms: Atrophy, Fat tissue decreased, Injection site nodule, Hypertrophy, Plaque, Calcification, Scar, Mass, Acquired lipodystrophy, or Skin fibrosis.
[108] Ulceration -- Subjects had an injection site reaction adverse event coded to at least one of these Preferred Terms: Injection site vesicles, Application site vesicles, Injection site erosion, Injection site ulcer, or Injection site scab

subjects. Injection site hair growth[109] occurred in 13 of 267 (4.9%) drisapersen 6 mg/kg/week subjects.

At the time of this review, skin biopsy results were available for 2 subjects:

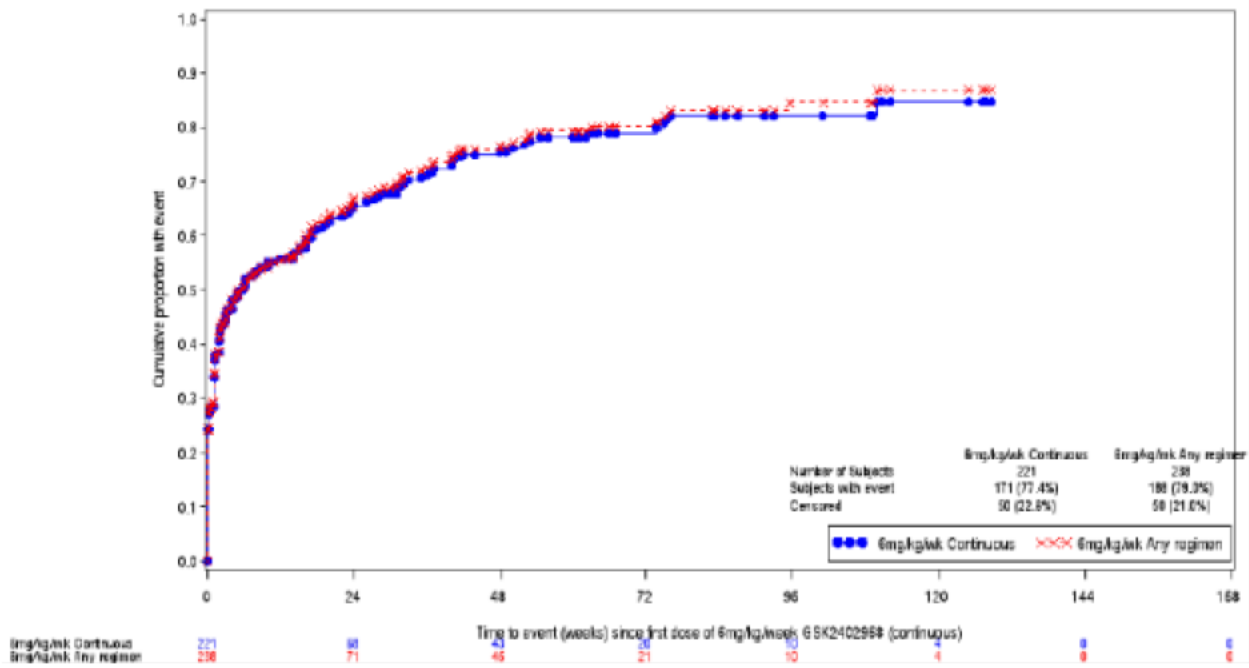
- DMD114349 Subject 576,[110] a 14 year old male from Germany treated with drisapersen 6 mg/kg/week from January 2011 to September 2013. While receiving drisapersen, moderate injections site discoloration and severe injection site induration of skin on his abdomen and thigh were reported. In March 2014 he had severe pain at the injection site. He was seen by a dermatologist in October 2014, who reported "irritating thickening mainly on the abdomen which increased in severity." Histological assessment on September 19, 2014 (1 year after cessation of drisapersen) reported "calcinosis of the skin with pathologic changes at the border of the biopsy tissue sample (obtained from the left upper arm). Treatment with pamidronate 30 mg i.v. was recommended by the dermatologist and it was also noted in the report that 'prior to this, treatment with diltiazem should be assessed'."
  Reviewer comment: This subject experienced severe injection site pain and skin thickening that was worsening 1 year after the cessation of drisapersen. Pathologic calcinosis was found on skin biopsy. No biopsy was performed at the main site of this subject's symptoms (abdomen).

- Study DMD114673) Subject 101,[111] a 9 year old male from the Netherlands, received 5 subcutaneous injections of drisapersen 0.5 mg/kg/week in Study PRO051-02 from May 5 to June 2, 2008. In extension study DMD114673, he received drisapersen 6 mg/kg via various dosing schedules starting in July 2009. Mild injection site reactions of erythema, hematoma, and induration were reported.
  In February 2011 a skin biopsy taken from a chronic injection site reaction revealed findings consistent with fibrosis and chronic inflammation described as "scleroderma-like reaction."[112] Immunohistochemical evaluation of the biopsy showed septal fibrosis and a predominantly mononuclear inflammatory infiltrate, again suggesting chronic inflammation.

The time to first injection site reaction is displayed in the figure below.

[109] Hair growth -- Subjects had an injection site reaction adverse event coded to at least one of these Preferred Terms: Hair growth, Hypertrichosis, or Hirsutism at injection site.
[110] Narrative on p. 4176-4178 120-day safety update report. Submitted to NDA 206031 on August 24, 2015.
[111] Narrative on p. 4192-4196 120-day safety update report. Submitted to NDA 206031 on August 24, 2015.
[112] Skin biopsy report. Submitted in Module 5.3.5.2 on 8/24/2015 to NDA 206031.

Figure 6. Cumulative distribution of time to first injection site reaction for subjects receiving drisapersen 6 mg/kg/week in DMD114349 (DMD114349 and parent studies)



Source: Sponsor Figure 5. P. 102 Summary of Clinical Safety

The table below summarizes the outcome and duration of injection site reactions in repeat dose studies. Of the 3872 injection site reaction events reported during drisapersen treatment, 795 (20.9%) events were reported as unresolved by the end of the studies. For resolved events for which the duration could be calculated, the mean duration of injection site reactions was 57.7 days (maximum duration 1217 days).

Table 32. Summary of outcome and duration of on-treatment injection site reaction events (repeat dose studies)

	Placebo N= 95	Drisapersen 3mg/kg/week N=17	Drisapersen 6mg/kg/week N=267	Drisapersen 6mg/kg intermittent N=38	Drisapersen all regimens N=285
Number of subjects (%)	21 (22.1)	11 (64.7)	210 (78.7)	31 (81.6)	224 (78.6)
Number of events	64	98	3477	261	3872
Outcomes, n (%)					
N	64	98	3451	224	3809
Recovered/resolved	58 (90.6)	66 (67.3)	2023 (58.6)	152 (67.9)	2275 (59.7)
Recovering/resolving	1 (1.6)	11 (11.2)	122 (3.5)	23 (10.3)	156 (4.1)
Not recovered/not resolved	1 (1.6)	5 (5.1)	739 (21.4)	49 (21.9)	795 (20.9)
Recovered/resolved with sequelae	4 (6.3)	16 (16.3)	567 (16.4)	0	583 (15.3)
Duration (days)					
N	61	82	2586	154	2855
n with missing data (including ongoing AEs)	3	16	891	107	1017
Mean (SD)	12.6 (9.18)	27.0 (22.89)	57.9 (128.99)	81.6 (176.86)	57.7 (129.81)
Median	13.0	21.5	14.0	10.0	14.0
Min, max	1, 57	3, 119	1, 1217	1, 801	1, 1217

Source: Sponsor Table 51. Summary of Clinical Safety

In the drisapersen 6 mg/kg/week group, AEs reported at least 5 times that were most frequently unresolved were: lipodystrophy acquired (81.0% unresolved), injection site atrophy (75.0% unresolved), injection site induration (56.9% unresolved), hyperaemia (50.0% unresolved), injection site nodule (45.5% unresolved), pigmentation disorder (42.9% unresolved), injection site discolouration (42.8% unresolved), and injection site reaction (25.5% unresolved).

For resolved events in the drisapersen 6 mg/kg/week group, the injection site reactions that had the longest mean durations included: fat tissue decreased (86.5 days; n=4), injection site erythema (57.8 days; n=953), injection site pain (59.6 days; n=173), injection site nodule (84.0 days; n=12), injection site discolouration (86.0 days; n=309), erythema (91.3 days; n=3), injection site reaction (116.6 days; n=195), injection site induration (143.7 days; n=76), injection site atrophy (270.3 days; n=12), lipodystrophy acquired (311.0 days; n=4), and injection site hypertrophy (323.0 days; n=3).

Medical photography is a standard method for documenting dermatologic conditions. No photographs of injection site reactions were prospectively collected and documented in any of the drisapersen studies included in the NDA. The only available photographs documenting injection site reactions were from 12 subjects in a DMD114673 substudy, who had a period of relatively intense subcutaneous administration exclusively in the abdomen from between approximately 50 and 72 weeks of weekly treatment.[113] These photographs are accompanied by limited documentation. The photographs shown below document injection site reactions at sites other than the abdomen, which were not subjected to relatively intense subcutaneous administration.

Reviewer comment: To maintain subject privacy, subject numbers and potentially identifying information (e.g., age, country of origin) are not included with these figures.

[113] Submitted to NDA 206031 on 6/19/2015.

Figure 7. Injection site reaction: Leg ulcer

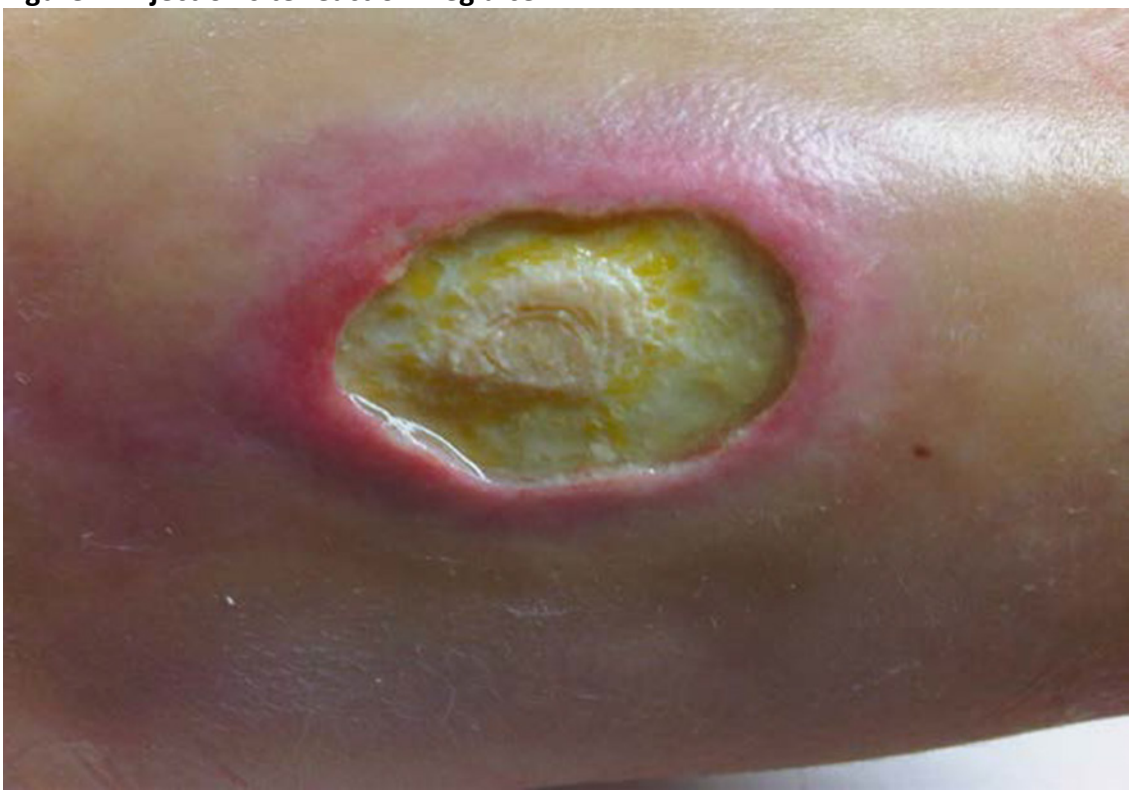


Figure 8. Injection site discoloration

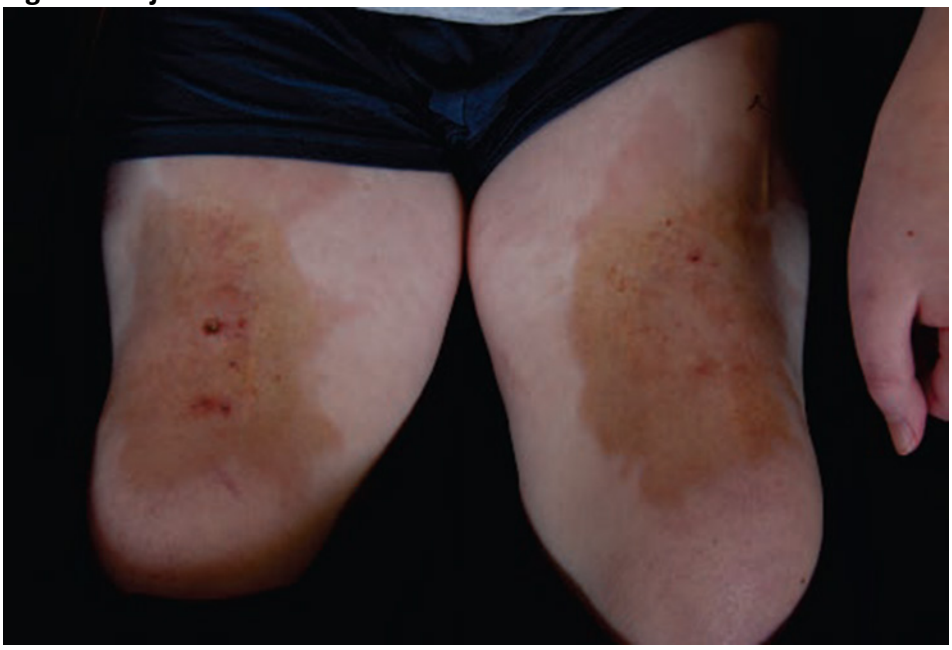
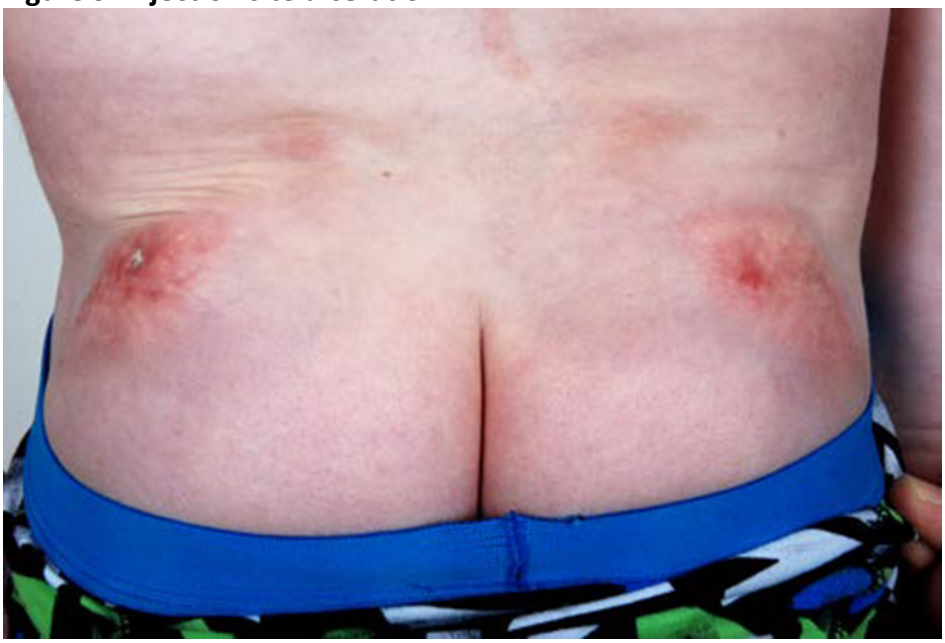


Figure 9. Injection site ulceration



Reviewer comment: At the time of this review, well-documented photographs of drisapersen injection site reactions are not available. The Division has asked the Sponsor to include medical photography as a part of standard documentation of moderate to severe injection site reactions in the limited number of subjects participating in ongoing studies. A report with this information is pending at the time of this review.

Reviewer conclusion

To facilitate proper administration of drisapersen, the Sponsor advises that dosing be performed by a medical professional. The Sponsor's proposed label provides detailed instructions, including guidelines for injection site rotation. Injection site rotation sites were added twice in the clinical program. The label administration instructions are the same as the last version of instructions in clinical studies. It is unclear whether there are any measures that can decrease the frequency or severity of injection site reactions with drisapersen.

8.5.4. **Inflammation**

In nonclinical studies, inflammatory effects of drisapersen were evident in mice and monkeys, impacting a multitude of organs and tissues and implicated in the majority of premature sacrifices or deaths. Inflammatory effects were evident at all dose levels in all species and were characterized by a dose related increase in (basophilic) granular/ vacuolated macrophages,

enlargement of lymphoid organs (spleen, lymph nodes) associated with lymphoid hyperplasia, and lymphocytic cell infiltrates in multiple tissues including at the site of injections. Changes were generally not associated with fibrosis, except at the injection sites following chronic dosing in mice and monkeys, and in the salivary glands in the monkey. Details of the mechanism of these inflammatory changes are not understood.

In three monkeys treated with drisapersen, high grade vascular changes consistent with those expected from complement-mediated effects were associated with thrombus formation resulting in myocardial infarction and early termination in two of these three monkeys.

The following laboratory markers of inflammation were measured in clinical studies: complement factor C3, haptoglobin, fibrinogen, high sensitivity C-reactive protein (hsCRP), immunoglobulin IgG, and Monocyte chemoattractant protein-1 (MCP-1). Inflammatory marker changes in placebo-controlled studies are summarized in the table below.

Table 33. Summary of inflammatory markers: baseline mean (SD) and mean (SD) changes from baseline at Weeks 24 and 48 (placebo-controlled studies)

	Placebo N=95		Drisapersen 3mg/kg/wk N=17		Drisapersen 6mg/kg/wk N=161		Drisapersen 6mg/kg intermittent [a] N=17		Drisapersen all regimens N=195	
Complement factor C3 (g/L)										
Baseline mean (SD)	n=95	1.235 (0.1982)	n=17	1.182 (0.2434)	n=161	1.269 (0.2223)	n=17	1.225 (0.2879)	n=195	1.257 (0.2306)
Week 24: Mean (SD) change	n=94	0.004 (0.2116)	n=15	-0.043 (0.1642)	n=159	-0.075 (0.2165)	n=17	-0.050 (0.1507)	n=191	-0.070 (0.2073)
Week 48: Mean (SD) change	n=77	-0.025 (0.1686)	NA	NA	n=137	-0.085 (0.2374)	n=15	-0.008 (0.1873)	n=152	-0.077 (0.2335)
Haptoglobin (g/L)										
Baseline mean (SD)	n=95	1.274 (0.3965)	n=17	1.182 (0.3762)	n=161	1.278 (0.4223)	n=17	1.205 (0.4406)	n=195	1.264 (0.4193)
Week 24: Mean (SD) change	n=93	0.016 (0.4068)	n=15	-0.087 (0.2973)	n=158	0.035 (0.3922)	n=17	-0.012 (0.3944)	n=190	0.021 (0.3856)
Week 48: Mean (SD) change	n=77	-0.005 (0.3901)	NA	NA	n=135	0.101 (0.4763)	n=15	0.103 (0.5553)	n=150	0.101 (0.4827)
Fibrinogen (g/L)										
Baseline mean (SD)	n=95	1.889 (0.4234)	n=17	1.714 (0.4989)	n=160	1.970 (0.4794)	n=17	2.004 (0.5379)	n=194	1.951 (0.4893)
Week 24: Mean (SD) change	n=91	0.044 (0.5656)	n=15	0.027 (0.5094)	n=155	0.118 (0.4987)	n=16	-0.106 (0.5457)	n=186	0.091 (0.5051)
Week 48: Mean (SD) change	n=78	0.041 (0.4662)	NA	NA	n=127	0.289 (0.6240)	n=15	0.140 (0.5060)	n=142	0.273 (0.6128)
hsCRP (mg/L)										
Baseline mean (SD)	n=95	0.51 (0.609)	n=17	0.58 (1.133)	n=161	0.82 (3.610)	n=17	3.55 (11.948)	n=195	1.03 (4.821)
Week 24: Mean (SD) change	n=93	0.39 (2.377)	n=15	-0.01 (1.068)	n=158	0.55 (4.593)	n=17	-2.85 (12.088)	n=190	0.20 (5.561)
Week 48: Mean (SD) change	n=78	0.48 (2.961)	NA	NA	n=135	0.83 (2.868)	n=15	-0.34 (14.353)	n=150	0.72 (5.185)
Immunoglobulin IgG (g/L)										
Baseline mean (SD)	n=95	7.948 (1.9785)	n=17	6.826 (1.8668)	n=161	7.664 (1.6923)	n=17	6.669 (1.6714)	n=195	7.504 (1.7327)
Week 24: Mean (SD) change	n=94	-0.170 (1.1140)	n=14	-0.315 (0.8670)	n=159	0.878 (1.4884)	n=17	0.636 (1.2840)	n=190	0.768 (1.4635)
Week 48: Mean (SD) change	n=78	-0.198 (1.3426)	NA	NA	n=136	1.786 (1.6481)	n=15	1.257 (1.8415)	n=151	1.734 (1.6692)
MCP-1 (ng/L)										
Baseline mean (SD)	n=82	805.12 (445.186)	n=17	931.18 (506.123)	n=148	915.62 (487.629)	n=4	703.55 (280.693)	n=169	912.16 (484.712)
Week 24: Mean (SD) change	n=80	18.21 (605.336)	n=15	-187.41 (556.790)	n=146	162.80 (623.632)	n=4	32.03 (340.773)	n=165	127.80 (618.750)
Week 48: Mean (SD) change	N=65	-87.83 (575.384)	NA	NA	n=123	305.08 (1073.622)	n=4	544.13 (660.044)	n=127	312.61 (1062.168)

Source: Table 84. Summary of Clinical Safety. Submitted to NDA 206031 on 4/27/2015.
Table includes data from studies DMD114117, DMD114044, and DMD114876 (first 24 weeks only).

Mean changes in complement C3 levels and haptoglobin were similar between drisapersen 6 mg/kg/week and placebo subjects. Mean values for fibrinogen were similar for drisapersen 6 mg/kg/week and placebo at baseline and at Week 12 and Week 24. At Week 48, mean change in fibrinogen was slightly higher at Week 48 in drisapersen subjects (0.289 g/L), compared to placebo subjects (0.04 g/L). Similar results were seen for immunoglobulin IgG.

For MCP-1, mean baseline values were similar for drisapersen 6 mg/kg/week and placebo. At Week 24 and Week 48, mean increases in this parameter were observed in subjects treated with drisapersen 6 mg/kg/week that were not seen in placebo-treated subjects. Mean baseline values for hsCRP were higher for drisapersen 6 mg/kg/week than for placebo. Mean increases were observed in both treatment groups at Week 12 that were larger for placebo than for drisapersen. At Week 24, the mean increases were similar in the two treatment groups and at Week 48, the mean increase with placebo was smaller than that seen with drisapersen.

The percentages of subjects with shifts from normal to high or low in complement C3 at each time point in the studies were similar for placebo and drisapersen at Week 12 and Week 24.[114] At Week 48, the percentage of subjects shifting from normal to low complement C3 was higher for drisapersen than for placebo (16 [11.7%] subjects versus 1 [1.3%] subject, respectively). At Week 48, there were 10 (8.1%) subjects in the drisapersen 6 mg/kg/week group with a shift from normal to high for MCP-1 compared with 1 (1.5%) subject in the placebo group.

In placebo-controlled studies inflammation adverse events occurred at similar rates in drisapersen 6 mg/kg/week subjects (29.8%), compared to placebo (27.4%) (see table below).

Table 34. Summary of on-treatment inflammation events by Preferred Terms (placebo-controlled studies)

Adverse event Preferred term	Placebo N=95 n (%)	Drisapersen 6mg/kg/wk N=161 n (%)
Any inflammation event	26 (27.4)	48 (29.8)
Pyrexia	21 (22.1)	41 (25.5)
Influenza like illness	2 (2.1)	2 (1.2)
Blood fibrinogen increased	1 (1.1)	2 (1.2)
Complement factor C3 decreased	0	2 (1.2)
Haptoglobin increased	3 (3.2)	1 (0.6)
Haptoglobin abnormal	0	1 (0.6)
Immunology test abnormal	0	1 (0.6)
Neutrophil toxic granulation present	1 (1.1)	0

Source: Sponsor Table 61. P. 125 Summary of Clinical Safety. Submitted to NDA 206031 on 4/27/2015.

Reviewer comment: There was 1 SAE in DMD114044 Subject 126 that was categorized as an inflammation event, coded to a PT 'Pyrexia.' The SAE occurred with an injection site reaction, as opposed to a more general process of inflammation.

Adverse event coding usually does not reflect a possible underlying inflammatory process. Thus, it is difficult to identify events through a search of specific MedDRA terms. This reviewer evaluated drisapersen adverse events for a possible inflammatory etiology.

[114] ISS Table 11.82

SAEs in drisapersen subjects that had or may have had an inflammatory etiology include the following:

- DMD114044 Subject 1111: PT Myocardial ischemia (possibly related to inflammation)
  This 6 year old male from Chile with no previous cardiac medical history and no relevant concomitant medications, had an SAE coded to the PT Myocardial ischemia. He had acute precordial chest pain, and ECG was reported as consistent with subendocardial ischemia. Cardiac enzymes were not performed. Echocardiogram was normal. ECG changes and chest pain resolved on the same day after a period of observation. Drisapersen was withheld for 4 weeks.
  Reviewer comment: This SAE is possibly related to drisapersen. Myocardial ischemia is rare in children. No structural cardiac abnormalities were reported on echocardiogram. He tested positive for anti-drisapersen antibodies.[115] *Inflammatory markers at the time of the event (April 20-25, 2012) were not measured. On May 9, 2012 he had an elevated sensitivity C-reactive protein (hsCRP) level of 7.9 mg/L.*[116- 117] *(It is unclear to what degree this laboratory value is drug related.) Prior to the SAE, this subject's hsCRP levels were 0.2-0.6 mg/L.*

- DMD114044 Subject 127: PT Intracranial venous sinus thrombosis (possibly related to inflammation)
  This event occurred in a 7 year old boy from Brazil. On 12/4/2012, high sensitivity C-reactive protein (hsCRP) was elevated at 9.5 mg/L. One week later, on Dec. 11, 2012 (6 months after his first dose of drisapersen), he developed a headache. Over the next few days, he developed seizures, strabismus, and severe thoraco-lumbar pain. A head CT showed hyperattenuating content partially filling the superior sagittal sinus and the straight sinus. Neurological assessment confirmed paralysis of cranial nerve VI (abducens) and signs of thrombosis of venous sinuses. The event of spinal pain was considered resolved on 1 February 2013, and the event of intracranial venous sinus thrombosis was considered resolved with sequelae (paralysis of the VI cranial nerve) on that same date.
  Reviewer comment: The cause of this SAE is unclear. Coagulation abnormalities have been reported with DMD.[118] *Fibrinogen, aPTT, INR, platelet count, and hemoglobin were normal. Conclusive anti-drisapersen antibody testing was not available.*[119] *High*

[115] P. 48 of the STD 2015-012 study report. Link located on p. 72 of the Summary of Clinical Pharmacology.
[116] Subject profile submitted to NDA 206031 on 4/27/2015. No laboratory range of normal values was provided.
[117] For all subjects, the Sponsor provided a normal range of 0-3 mg/L for hsCRP. This is an adult reference range, because a reference range for ages 0-17 has not been established (Sponsor 9/21/2015 submission to NDA 206031).
[118] Toshio Saito (2014). Coagulation and Fibrinolysis Abnormalities in Patients with Muscular Dystrophy, Fibrinolysis and Thrombolysis, Dr. Krasimir Kolev (Ed.), ISBN: 978-953-51-1265-5, InTech, DOI: 10.5772/57411. Available from: http://www.intechopen.com/books/fibrinolysis-and-thrombolysis/coagulation-and-fibrinolysis-abnormalities-in-patients-with-muscular-dystrophy
[119] P. 48 of the STD 2015-012 study report. Link located on p. 72 of the Summary of Clinical Pharmacology.

sensitivity C-reactive protein was elevated 1 week prior to the onset of headache. It is unclear whether drug-related inflammation may have contributed to this event.

- DMD 114349 Subject 1310: PT Small intestinal obstruction (inflammatory changes seen in the duodenum and colon)
  The first drisapersen dose for this 8 year old boy from Canada was August 3, 2011 in Study 114044. On Oct. 10, 2011 he had an AE of abdominal pain. He had gastrointestinal AEs intermittently throughout Study 114044 (e.g., abdominal pain, vomiting diarrhea). In Study 114349 (June 10, 2013), he had a partial small bowel obstruction. He underwent endoscopy and colonoscopy under general anesthesia. Biopsies of the duodenum, stomach, distal esophagus, and colon showed non-specific inflammatory changes in the duodenum, possibly drug-related or infectious in nature. No inflammatory changes were noted in the large bowel. Endoscopy revealed evidence of mild esophagitis, gastritis associated with ulceration and erosions, and duodenitis. The gastric erosions were suggested to be secondary to steroid use. There was evidence of moderate patchy colitis in about 1/3 of the colon, suggestive of a diffuse inflammatory or infective process. No evidence of mycoplasmal or mycobacterial infection was noted.
  Haptoglobin results were normal in this subject. On the measurement prior to the event (May 8, 2013; 33 days prior), High sensitivity C-Reactive protein (hsCRP) was 2.3 mg/L, which was an increase from previous values which ranged from 0.2 – 0.9 mg/L. No complement factor C3, IgG, and MCP-1 results were provided for this subject.

- DMD114673 Subject 105: PT Convulsion (possible contribution of drug-related inflammation)
  On (b) (6), 2 days after his latest dose of drisapersen, this 8 year old male from Belgium developed a fever of 39.5°C. Four hours later he had a generalized seizure, which lasted 20 minutes. He was hospitalized. Viral swab was positive for H1N1 influenza A. No action was taken with drisapersen treatment.
  Reviewer comment: This subject's seizure is likely related to his fever and H1N1 influenza A infection, which can lead to seizures (with or without fever).[120-121] *An inflammatory effect (e.g., cerebral vasculitis) of drisapersen contributing to this seizure is possible. Clonic seizures occurred in nonclinical studies.*

- DMD114117 Subject 2132: PT Myocarditis. (possible contribution of drug-related inflammation)
  In November 2011, this 6 year old boy from Spain, had chest pain and was diagnosed with myocarditis. Serology results for coxsackie virus, performed on December 16, 2011, were: coxsackie virus IgG 396 U/mL (normal range: 80 – 100); and coxsackie virus IgM

[120] Pinki,S, et al. "Neurological complications of pandemic influenza A H1N1 2009 infection: European case series and review." European journal of pediatrics 170.8 (2011): 1007-1015.
[121] The event is consistent with a complex febrile seizure, given the subject's age and the long seizure duration of 20 minutes.

45 U/mL (normal range: 30 – 50).[122] No action was taken with drisapersen in response to this myocarditis event. The event was reported to be resolved with sequelae. (Sequelae were not reported.)[123]
Reviewer comment: This subject had an SAE of myocarditis in the setting of a positive coxsackie virus serology. Myocarditis is a rare event in children. This event may be an event of viral myocarditis. An inflammatory drug effect is also a possible cause. The event was reported as resolved while the patient continued drisapersen treatment.

Reviewer conclusion:

Larger changes in inflammatory markers MCP-1, complement C3, and hsCRP occurred in drisapersen subjects, compared to placebo. Some SAEs in drisapersen subjects had or may have had an inflammatory etiology. Elevations in hsCRP were associated with some events. However, hsCRP is a nonspecific marker of inflammation and can be elevated for a variety of reasons. The utility of hsCRP in predicting drug-related inflammatory events is unclear.

This reviewer supports describing preclinical and clinical inflammation findings in the product label. If a patient has inflammatory changes after drisapersen treatment, withholding treatment may be considered if the risk outweighs the benefit.

8.5.5. **Coagulation disorders**

In drisapersen preclinical studies, vascular thrombosis and inflammation occurred in some animals that died prematurely.

Sheehan and Lan[124] published a study that demonstrated aPTT prolongation (using in vitro coagulation assays in human plasma and purified enzyme systems) with ISIS 2302, which, like drisapersen, is a phosphorothioate oligonucleotide. In this study, ISIS 2302 showed partial inhibition of intrinsic tenase activity, which was oligonucleotide sequence–independent but required the phosphorothioate backbone. The authors suggested that inhibition of intrinsic tenase is a general property of phosphorothioate oligonucleotides.

[122] Sponsor IR response submitted to NDA 206031 on 10/5/2015.
[123] Sponsor IR response submitted to NDA 206031 on 9/22/2015.
[124] Sheehan JP1, Lan HC. Phosphorothioate oligonucleotides inhibit the intrinsic tenase complex. *Blood.* 1998 Sep 1;92(5):1617-25.

Based on this preclinical and in vitro data, coagulation disorders have been an area of clinical safety concern during the drisapersen clinical development program. Coagulation abnormalities have been reported with DMD.[125]

In placebo-controlled studies, coagulation abnormalities were reported in 13 of 161 (8.1%) drisapersen subjects, compared to 14 of 95 (14.7%) placebo subjects. In repeat dose studies, coagulation abnormalities were reported in 33 of 285 (11.6%) drisapersen subjects. Two (0.7%) drisapersen subjects had coagulation abnormality SAEs, and 2 (0.7%) subjects experienced severe coagulation abnormality AEs; these AEs were related to laboratory abnormalities and are described below.

Table 35. Summary of coagulation abnormality adverse events (repeat dose studies)

Adverse event	Placebo N=95 n (%)	Drisapersen 3mg/kg/wk N=17 n (%)	Drisapersen 6mg/kg/wk N=267 n (%)	Drisapersen 6mg/kg interm ttent N=38 n (%)	Drisapersen all regimens N=285 n (%)
Any coagulation abnormality	14 (14.7)	0	32 (12.0)	1 (2.6)	33 (11.6)
Any coagulation abnormality SAE	0	0	2 (0.7)	0	2 (0.7)
Any severe coagulation abnormality	0	0	2 (0.7)	0	2 (0.7)

Source: Sponsor Table 63. Summary of Clinical Safety

The most commonly reported coagulation abnormality adverse events were International normalized ratio increased, Blood fibrinogen decreased, Prothrombin time prolonged, Activated partial thromboplastin time prolonged, and Fibrin D dimer increased (see table below).

Table 36. Summary of coagulation abnormality adverse events by Preferred Term (repeat dose studies)

Adverse event preferred term	Placebo N=95 n (%)	Drisapersen 3mg/kg/wk N=17 n (%)	Drisapersen 6mg/kg/wk N=267 n (%)	Drisapersen 6mg/kg intermittent[a] N=38 n (%)	Drisapersen all regimens[b] N=285 n (%)
Any coagulation AE	**14 (14.7)**	**0**	**32 (12.0)**	**1 (2.6)**	**33 (11.6)**
International normalised ratio increased	4 (4.2)	0	11 (4.1)	1 (2.6)	12 (4.2)
Blood fibrinogen decreased	7 (7.4)	0	11 (4.1)	0	11 (3.9)
Prothrombin time prolonged	4 (4.2)	0	7 (2.6)	0	7 (2.5)
Activated partial thromboplastin time prolonged	3 (3.2)	0	6 (2.2)	1 (2.6)	7 (2.5)
Fibrin D dimer increased	2 (2.1)	0	6 (2.2)	0	6 (2.1)
Fibrin degradation products increased	0	0	2 (0.7)	0	2 (0.7)
Coagulation time prolonged	2 (2.1)	0	1 (0.4)	0	1 (0.4)
Activated partial thromboplastin time abnormal	1 (1.1)	0	1 (0.4)	0	1 (0.4)
Activated partial thromboplastin time	0	0	1 (0.4)	0	1 (0.4)
Bleeding time prolonged	0	0	1 (0.4)	0	1 (0.4)
Blood test abnormal	0	0	1 (0.4)	0	1 (0.4)

[125] Toshio Saito (2014). Coagulation and Fibrinolysis Abnormalities in Patients with Muscular Dystrophy, Fibrinolysis and Thrombolysis, Dr. Krasimir Kolev (Ed.), ISBN: 978-953-51-1265-5, InTech, DOI: 10.5772/57411. Accessed on 09/25/2015 at : http://www.intechopen.com/books/fibrinolysis-and-thrombolysis/coagulation-and-fibrinolysis-abnormalities-in-patients-with-muscular-dystrophy

Coagulation test abnormal	0	0	1 (0.4)	0	1 (0.4)
Blood fibrinogen	1 (1.1)	0	0	0	0
Fibrin degradation products	1 (1.1)	0	0	0	0
Hypofibrinogenaemia	0	0	1 (0.4)	0	1 (0.4)

Source: Sponsor Table 64. Summary of Clinical Safety

Standardised MedDRA Queries (SMQs)

In a search of repeat dose studies using the MedDRA Embolic and Thrombotic SMQ, 1 subject had an AE; this subject (Study 114044 subject 1270, treated with drisapersen 6 mg/kg/week) experienced an SAE of Intracranial venous sinus thrombosis (discussed in detail in Section 8.4.2). The subject was withdrawn from study treatment.

Reviewer comment: The mechanism for this subject's intracranial venous sinus thrombosis is unclear. Fibrinogen, aPTT, INR, platelet count, and hemoglobin were normal. Conclusive anti-drisapersen antibody testing was not available.[126] *High sensitivity C-reactive protein was elevated 1 week prior to the onset of headache. It is unclear whether drug-related inflammation may have contributed to this event.*

DMD114044 subject 527 experienced glomerulonephritis with renal venous thrombosis and pulmonary emboli. Renal vein thrombosis and pulmonary emboli were not coded separately from his overall diagnosis of glomerulonephritis, so the events were not detected by the SMQ search. (See Section 8.5.2for a detailed description of this subject.)

In a search of repeat dose studies using the MedDRA Haemorrhages SMQ, events were reported for 154 of 285 (56.8%) drisapersen 6 mg/kg/week subjects, compared to 40 of 95 (42.1%) placebo subjects. Preferred terms with an increased frequency in drisapersen subjects compared to placebo included Haematuria and Injection site haematoma; after adjusting for treatment exposure, the incidence rate of these Preferred Terms per 100 subject-years remained increased in drisapersen subjects.[127] Preferred terms Injection site bruising and Epistaxis were also more frequent in drisapersen subjects compared to placebo subjects; however, after adjusting for treatment exposure, incidence rates for these PTs were similar in drisapersen and placebo subjects. The rates of other Preferred Terms in the MedDRA Haemorrhages SMQ were similar between drisapersen and placebo subjects.

The only hemorrhage SMQ AE categorized as a Serious occurred in drisapersen-treated Subject 3000 (PT Haematuria). This SAE was related to anesthesia-associated rhabdomyolysis and was not drisapersen-related. (See Renal Toxicity Section 8.5.2 for additional details.)

Some hemorrhage SMQ adverse events in drisapersen subjects occurred as part of SAEs of immune thrombocytopenia. However, they were not categorized as SAEs themselves.

[126] P. 48 of the STD 2015-012 study report. Link located on p. 72 of the Summary of Clinical Pharmacology.
[127] Sponsor Table 35. Summary of Clinical Safety p. 72-73.

Reviewer comment:

MedDRA Haemorrhages SMQ Preferred Terms with an increased frequency in drisapersen subjects compared to placebo, after adjusting for treatment exposure, were Haematuria and Injection site haematoma. These events were associated with drisapersen safety issues of renal toxicity and injection site reactions. In addition, there were some bleeding adverse events associated with SAEs of immune thrombocytopenia. The frequencies of other hemorrhage SMQ events were similar in drisapersen and placebo subjects.

This reviewer concludes that increased frequency of hemorrhage SMQ events with drisapersen subjects occurred with drisapersen safety issues, including renal toxicity, injection site reactions, and thrombocytopenia.

Laboratory data

In analyses of changes from baseline to Week 48, mean changes in aPTT and INR[128] were seen which were similar for drisapersen and placebo.[129] Mean change from baseline to Week 48 in aPTT was -2.5 seconds in drisapersen 6 mg/kg/week subjects, compared to 0.3 seconds in placebo subjects. Mean change from baseline to Week 48 in INR was -0.1 in drisapersen 6 mg/kg/week subjects, compared to 0.1 in placebo subjects.

Shifts from baseline to worst post-treatment value[130] were similar in drisapersen and placebo subjects (see table below).

[128] Integrated Summary of Safety documents and datasets included the following terminology: "PTT (INR)", "PTT (INR) ratio", "Activated Partial Thromboplastin Time ratio (INR)" or "Activated Partial Thromboplastin Time ratio." In its response to an FDA information request (submitted to NDA 206031 on September 10, 2015) BioMarin confirmed that such terminology "all refer exclusively to INR calculated from prothrombin time (PT)."
[129] ISS Table 11.77
[130] Categorized according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0. NIH publication # 09-7473. May 29, 2009.

Table 37. Shift from baseline to worst post-treatment aPTT measurement based on CTCAE grade. Placebo-Controlled Studies

Laboratory Test Name / Treatment Group / Worst Post-Treatment CTCAE Grade	Baseline CTCAE Grade 0	1	2	3	4	Total
aPTT increased						
Placebo (n=95)						
0	42 (44.2%)	0	0	0	0	42
1	37 (38.9%)	8 (8.4%)	0	0	0	45
2	3 (3.2%)	3 (3.2%)	0	0	0	6
3	1 (1.1%)	0	0	1 (1.1%)	0	2
4	0	0	0	0	0	0
Total	83	11	0	1	0	95
6 mg/kg/week Drisapersen (n=162)						
0	85 (52.5%)	2 (1.2%)	0	0	0	87
1	51 (31.5%)	15 (9.3%)	0	0	0	66
2	4 (2.5%)	2 (1.2%)	1 (0.6%)	0	0	7
3	1 (0.6%)	1 (0.6%)	0	0	0	2
4	0	0	0	0	0	0
Total	141	20	1	0	0	162
INR						
Placebo (n=95)						
0	10 (10.5%)	0	0	0	0	10
1	54 (56.8%)	20 (21.1%)	1 (1.1%)	0	0	75
2	3 (3.2%)	1 (1.1%)	0	0	0	4
3	3 (3.2%)	3 (3.2%)	0	0	0	6
4	0	0	0	0	0	0
Total	70	24	1	0	0	95
6 mg/kg/week Drisapersen (n=162)						
0	8 (4.9%)	0	0	0	0	8
1	110 (67.9%)	20 (12.3%)	0	1 (0.6%)	0	131
2	8 (4.9%)	5 (3.1%)	3 (1.9%)	0	0	16
3	4 (2.5%)	2 (1.2%)	0	1 (0.6%)	0	7
4	0	0	0	0	0	0
Total	130	27	3	2	0	162

Source: Sponsor Table 10.1. Submitted to NDA 206031 on July 20, 2015.

Three subjects (Study DMD114349 Subjects 505, 687 and 2000, all treated with drisapersen 6 mg/kg/week) met the stopping criteria for disseminated intravascular coagulation (DIC); these subjects had a thrombocyte count <75 x 10^9/L and either fibrin split product test or D-dimer above the upper limit of the normal range. Disseminated intravascular coagulation was not confirmed in any of these subjects. These subjects are described in detail in the Thrombocytopenia Section 8.5.1. Anti-platelet antibodies were confirmed in Subjects 505 and 2000.

Reviewer comment: Testing for disseminated intravascular coagulation (DIC) was performed to evaluate for potential causes for thrombotic lesions in drisapersen preclinical studies.[131] *No cases of DIC were identified in preclinical studies of drisapersen. The drisapersen clinical studies do not provide evidence of DIC with drisapersen.*

Two (0.7%) drisapersen 6 mg/kg/week subjects experienced coagulation abnormality events that were SAEs:

[131] Consult review by Dr. Shashaty 05/05/2010.

- DMD114349 Subject 624 had an SAE with a PT Alanine aminotransferase increased. AST and ALT were not significantly different from baseline. GGT and bilirubin measurements were normal. He had one INR measurement of 6.2 on September 11, 2013. According to the narrative, the lab reported that the elevated INR may have resulted from clinical or sample integrity problems. Other INR values were 1.2, which was his baseline value. *There were no clinically significant changes in hepatic laboratory measurements, except for one increased INR measurement. The increased INR measurement resolved without treatment. The patient had no symptoms of coagulopathy.*

- DMD114044 Subject 37 had an SAE with a PT Alanine aminotransferase increased. [132] He had no change in clinical status. His laboratory measurements are summarized in the table below:

Table 38. DMD114044 Subject 37 Hepatic laboratory measurements

Date	ALT (IU/L)	AST (IU/L)	ALP (IU/L)	GGT (IU/L)	LDH (IU/L)	Total Bilirubin (µmol/L)	Total Protein (g/L)	INR
Normal	*0-45*	*0-42*	*60-415*	*0-65*	*0-250*	*0-22*	*55-80*	*0.9-1.1*
29 Sep 2011 (Baseline)	425	323	124	11	1195	4	65	1.1
13 Oct 2011	**627**	**270**	**123**	**10**	**1521**	**5**	**68**	**2.2**
27 Oct 2011	**426**	**181**	**120**	**9**	**918**	**4**	**67**	**2.4**
8 Nov 2011	467	437	108	-	-	5	-	-
10 Nov 2011	449	208	113	10	1056	5	71	1.0
	466	213	114			4		
24 Nov 2011	304	168	116	10	781	5	67	1.2

Reviewer comment: The subject had increased ALT and INR without clinical symptoms. GGT remained normal.

Two (0.7%) drisapersen 6 mg/kg/week subjects experienced coagulation abnormality events that were categorized as severe:

- DMD114349 Subject 526, an 8 year old boy from France, who had severe adverse events of aPTT prolonged, International normalised ratio increased, and Prothrombin time prolonged. He had an elevated INR (1.4; normal range 0.9 – 1.1) and a normal aPTT pre-treatment at screening.
  He was treated with drisapersen 6 mg/kg/week in study DMD114044 from January 3, 2011 to November 28, 2011. He received open-label drisapersen at 6 mg/kg/week from January 3, 2012 in study DMD114349. On July 19, 2013, INR was 5.5 and aPTT was 54

[132] ISS p. 3824.

seconds. Dosing with drisapersen was interrupted. On 7/23/2013, INR and aPTT were similar to his baseline levels (see table below).

Table 39. Subject 526 aPTT and INR measurements

Test date	INR	aPTT	Notes
12/7/2010	1.4	29	Screening
1/3/2011	1.3	28	Baseline
1/17/2011	1.7	31	
2/28/2011	1.4	28	
3/28/2011	1.5	30	
4/26/2011	1.8	44	
5/9/2011	1.4	30	
6/21/2011	1.5	29	
8/16/2011	1.5	25	
10/10/2011	1.5	29	
12/6/2011	1.5	31	
1/3/2012	1.5	30	
2/27/2012	1.4	27	
3/26/2012	1.4	28	
4/23/2012	1.3	28	
5/21/2012	1.3	27	
6/19/2012	1.4	27	
8/13/2012	1.3	28	
10/8/2012	1.4	26	
12/4/2012	1.5	28	
1/28/2013	1.5	27	
3/25/2013	1.4	28	
5/21/2013	1.5	27	
7/15/2013	5.5	54	Measurements corresponding to the reported Severe adverse events
7/23/2013	1.5	30	
7/30/2013	1.6	29	
8/6/2013	1.7	40	
9/10/2013	1.6	32	

Source: ISS datasets
Normal laboratory range INR: 0.9-1.1
Normal laboratory range aPTT: 22-34 seconds

Reviewer comment: The cause of this subject's elevations in aPTT and INR in July 2013 is unclear. There were no adverse events that provide a possible explanation for the aPTT and INR results.

- Study DMD114349 Subject 000511, a 9 year old boy from France, had severe adverse events of Fibrin degradation products increased and Fibrin D-dimer increased. He started treatment with drisapersen 6 mg/kg/week in study DMD114044 on March 24, 2011. He started open-label drisapersen in study DMD114349 at 6 mg/kg weekly on March 2012. He was hospitalized for severe injection site edema on the back of his upper arm on (b) (6). On September 4, 2013, he developed a severe AE coded as 'Fibrin degradation products increased,' and on September 19, 2013, he had an increase in fibrin D-dimer. The events were not resolved by the end of the study. *Reviewer comment: It is possible that this subject's increase in fibrin degradation products, including D-dimer, were related to drisapersen. No baseline values were provided, so the change after starting drisapersen treatment could not be assessed.*

Reviewer conclusion and recommendations:

Sheehan and Lan[133] reported inhibition of intrinsic tenase and aPTT prolongation (using in vitro coagulation assays in human plasma and purified enzyme systems) with ISIS 2302, which, like drisapersen, is a phosphorothioate oligonucleotide. In clinical studies, some drisapersen subjects had increases in aPTT and INR without a clear cause. However, the frequencies of abnormal aPTT and PT measurements were similar in placebo and drisapersen subjects. An increased frequency of hemorrhage SMQ events with drisapersen subjects occurred with drisapersen safety issues, including renal toxicity, injection site reactions, and thrombocytopenia.

In drisapersen preclinical studies, vascular thrombosis and inflammation occurred in some animals that died prematurely. In clinical studies, the 2 cases of thrombosis (1 case of intracranial venous sinus thrombosis with normal aPTT and INR measurements and one case of thromboemboli related to glomerulonephritis and nephrotic syndrome) were not accompanied by changes in coagulation factors.

If drisapersen is approved, we will continue to evaluate cases of thrombosis, as well as related safety issues, including inflammation, renal toxicity, and immunogenicity. This reviewer supports describing the preclinical findings of vascular thrombosis and inflammation, as well as the case of intracranial venous sinus thrombosis in the Warnings and Precautions section of the prescribing information.

[133] Sheehan JP1, Lan HC. Phosphorothioate oligonucleotides inhibit the intrinsic tenase complex. *Blood.* 1998 Sep 1;92(5):1617-25.

8.5.6. Hepatic toxicity

The liver is considered a target organ of drisapersen, because most antisense oligonucleotides accumulate in the liver. Because it is deposited in the liver, drisapersen has the potential for hepatotoxicity.

Liver function tests that are most frequently evaluated (AST, ALT, and LDH) are commonly elevated in patients with DMD. With muscle degeneration, substantial quantities of these enzymes can be released from cardiac and skeletal muscle.[134] Liver enzyme elevations are often greater than 5x ULN, persist for years, and tend to be highest at a younger age in DMD patients. Gamma-glutamyl transferase (GGT) is a membrane bound enzyme produced primarily in the liver, with little or none produced from human skeletal muscle. GGT has been shown to be normal in DMD patients. In addition, the total bilirubin levels remain normal in DMD patients.

In repeat dose studies, hepatic toxicity adverse events were reported for 28 (10.5%) subjects treated with drisapersen 6 mg/kg/week (see tables below). The most commonly reported hepatic toxicity AE was glutamate dehydrogenase increased. In placebo controlled studies, the most commonly reported hepatic toxicity AE was also glutamate dehydrogenase increase (2.5% for drisapersen vs 0% for placebo).

Table 40. Summary of hepatic toxicity adverse events (on treatment in repeat dose studies)

Adverse event	Placebo N=95 n (%)	Drisapersen 3mg/kg/wk N=17 n (%)	Drisapersen 6mg/kg/wk N=267 n (%)	Drisapersen 6mg/kg interm ttent N=38 n (%)	Drisapersen all regimens N=285 n (%)
Any hepatic abnormality	2 (2.1)	0	28 (10.5)	7 (18.4)	31 (10.9)
Any hepatic abnormality SAE	0	0	4 (1.5)	0	4 (1.4)
Any severe hepatic abnormality	0	0	1 (0.4)	0	1 (0.4)
Any hepatic abnormality leading to withdrawal	0	0	0	0	0

Source: Summary of Clinical Safety Table 67
Includes data from studies DMD114117, DMD114044, DMD114876, DMD114349, PRO051-02, and DMD114673.

[134] Koronoes D, Brown,M, Palis M, "'Liver Function Tests' Are Not Always Tests of Liver Function," *American Journal of Hematology*, Vol. 66 (2001): 46-48.

Table 41. Hepatic toxicity adverse event by MedDRA Preferred Term (on treatment in repeat dose studies)

Adverse event preferred term	Placebo N=95 n (%)	Drisapersen 3mg/kg/wk N=17 n (%)	Drisapersen 6mg/kg/wk N=267 n (%)	Drisapersen 6mg/kg interm ttent N=38 n (%)	Drisapersen all regimens N=285 n (%)
Any hepatic abnormality AE	**2 (2.1)**	**0**	**28 (10.5)**	**7 (18.4)**	**31 (10.9)**
Glutamate dehydrogenase increased	0	0	13 (4.9)	5 (13.2)	16 (5.6)
Alanine aminotransferase increased	2 (2.1)	0	7 (2.6)	0	7 (2.5)
Gamma-glutamyltransferase increased	0	0	7 (2.6)	2 (5.3)	7 (2.5)
Alanine aminotransferase	0	0	1 (0.4)	0	1 (0.4)
Aspartate aminotransferase increased	0	0	1 (0.4)	0	1 (0.4)
Transaminases increased	0	0	1 (0.4)	0	1 (0.4)
Ultrasound liver abnormal	0	0	1 (0.4)	0	1 (0.4)
Hepatic function abnormal	0	0	1 (0.4)	0	1 (0.4)
Hepatic steatosis	0	0	1 (0.4)	0	1 (0.4)
Hepatocellular injury	0	0	1 (0.4)	0	1 (0.4)
Hepatomegaly	0	0	1 (0.4)	0	1 (0.4)
Hepatotoxicity	0	0	1 (0.4)	0	1 (0.4)
Liver disorder	0	0	1 (0.4)	0	1 (0.4)
Hepatitis	1 (1.1)	0	0	0	0

Source: Summary of Clinical Safety Table 68
Includes data from studies DMD114117, DMD114044, DMD114876, DMD114349, PRO051-02, and DMD114673.

Hepatic laboratory data

Mean baseline values for GGT were similar for drisapersen 6 mg/kg/week and placebo. Mean increases from baseline in GGT were larger for drisapersen than for placebo. For drisapersen 6 mg/kg/week subjects, the mean change in GGT from baseline was 2.9 IU/L at Week 12, 8.2 IU/L at Week 24, and 16.6 IU/L at Week 48, compared -0.1, -0.2, and 0.9 IU/L, respectively, in placebo subjects. In placebo-controlled studies, Grade 1[135] and Grade 2 increases in GGT occurred in 10 (5.1%) and 7 (3.6%) drisapersen subjects,[136] respectively. All subjects had normal GGT values at baseline. None of the 95 placebo subjects had any abnormal GGT values.

Mean increases in glutamate dehydrogenase (GLDH) from baseline were larger for drisapersen than for placebo. For drisapersen 6 mg/kg/week the mean change from baseline was 1.29 U/L at Week 12, 2.14 U/L at Week 24, and 3.59 U/L at Week 48, compared to 0.22, 0.09, and -0.04 U/L, respectively, for placebo. In placebo-controlled studies, 89 of 139 (54.9%) drisapersen 6 mg/kg/week subject had a shift from baseline normal to post-treatment high GLDH, compared to 26 of 87 (27.4%) placebo subjects.[137]

Only small mean changes in bilirubin values (total and direct) were observed for both

[135] CTCAE Grade 1 = >ULN - 2.5 x ULN; CTCAE Grade 2 = >2.5 - 5.0 x ULN
[136] P. 62-63 ISS addendum submitted to NDA 206031 on 7/20/2015.
[137] P. 83-84 ISS addendum submitted to NDA 206031 on 7/20/2015.

drisapersen 6 mg/kg/week and for placebo. In placebo-controlled studies, 2 of 194 (1.0%) drisapersen subject and 1 of 94 (1.1%) placebo subject had a shift from baseline normal to Grade 1 increased blood bilirubin (>ULN - 1.5 x ULN).[138] No subjects in any group had a shift in blood bilirubin greater than Grade 1.

There were no cases of Hy's law drug-induced liver injury (ALT increases ≥3 x ULN with concomitant elevations in total bilirubin ≥2 x ULN) during treatment in the drisapersen clinical program.

There were 4 hepatic SAEs in drisapersen subjects:

- DMD114349 Subject 624 had an SAE with a PT Alanine aminotransferase increased. AST and ALT were not significantly different from baseline. GGT and bilirubin measurements were normal. He had one INR measurement of 6.2 on September 11, 2013. According to the narrative, the lab reported that the elevated INR may have resulted from clinical or sample integrity problems. Other INR values were 1.2, which was his baseline value. *ad no symptoms of coagulopathy.*
- DMD114044 Subject 37 had an SAE with a PT Alanine aminotransferase increased. [139] He had no change in clinical status. His laboratory measurements are summarized in the table below:

Table 42. DMD114044 Subject 37 hepatic laboratory measurements

Date	ALT (IU/L)	AST (IU/L)	ALP (IU/L)	GGT (IU/L)	LDH (IU/L)	Total Bilirubin (µmol/L)	Total Protein (g/L)	INR
Normal	*0-45*	*0-42*	*60-415*	*0-65*	*0-250*	*0-22*	*55-80*	*0.9-1.1*
29 Sep 2011 (Baseline)	425	323	124	11	1195	4	65	1.1
13 Oct 2011	**627**	**270**	**123**	**10**	**1521**	**5**	**68**	**2.2**
27 Oct 2011	**426**	**181**	**120**	**9**	**918**	**4**	**67**	**2.4**
8 Nov 2011	467	437	108	-	-	5	-	-
10 Nov 2011	449	208	113	10	1056	5	71	1.0
	466	213	114			4		
24 Nov 2011	304	168	116	10	781	5	67	1.2

Reviewer comment: The subject had increased ALT and INR without clinical symptoms. GGT remained normal.

[138] P. 59-60 ISS addendum submitted to NDA 206031 on 7/20/2015.
[139] ISS p. 3824.

- DMD114349 Subject 516 had an SAE with a PT Hepatocellular injury. He had hemolytic anemia and hepatocellular injury with mycoplasma infection.
  Reviewer comment: Hepatic abnormalities can occur with mycoplasma infection. It is unclear whether hepatic toxicity related to drisapersen contributed to his hepatic abnormalities. For details on this case, see Section 8.4.2.

- DMD114349 Subject 1281 had an SAE with a PT Hepatic abnormality. This 8-year-old subject was treated with placebo from 11 June 2012 to 09 May 2013 in study DMD114044. He started treatment with open-label drisapersen 6 mg/kg/week from 11 June 2013. On 25 June 2013, 14 days after the start of drisapersen, the subject developed grade 2 or moderate liver toxicity. The subject presented with international normalized ratio greater than 1.5 and ALT greater than 8xULN. Other relevant tests included an abdominal ultrasound which showed no change. Treatment with drisapersen was interrupted on 25 June 2013. The event resolved on 22 July 2013. Treatment with drisapersen was re-started on 29 July 2013. The event did not recur.
  Reviewer comment: No alternate etiology for this subject's liver toxicity was reported. Considering the accumulation of drisapersen in liver tissue, it is possible that this event is related to drisapersen.

Conclusion and monitoring recommendation

Phosphorothioate oligonucleotides are known to accumulate in the liver, and hepatic toxicity occurred in 10.5% subjects treated with drisapersen 6 mg/kg/week.
The Sponsor's proposed labeling related to hepatic laboratory monitoring and treatment stopping criteria is displayed below:

Label Section 2.2 Monitoring to Assess Safety

Elevations in Liver Enzymes [see Adverse Reactions (6.1)]
Conduct liver function tests prior to initiating [TRADENAME] treatment to assess baseline levels. Monitoring of liver function tests once every 6 months is recommended during [TRADENAME] treatment. Interrupt [TRADENAME] treatment if one or more of the following abnormalities are observed:

- Bilirubin 2 x ULN
- INR >1.5
- GGT >2 x ULN
- Symptoms of hepatitis (e.g., onset or worsening of nausea, anorexia, jaundice or abdominal pain) or hypersensitivity (fever, rash, eosinophilia)

Reviewer comment: This reviewer supports measurement of liver function tests, including GGT, bilirubin, and INR monthly, instead of every 6 months as proposed by the Sponsor. For most of the Phase 3 study, liver function tests were monitored monthly. This reviewer agrees with the Sponsor's proposed treatment stopping criteria based on liver function tests, which were used in clinical studies.

8.6. Specific Safety Studies/Clinical Trials

No specific safety studies were performed in the drisapersen clinical development program.

8.7. Additional Safety Explorations

8.7.1. Human Carcinogenicity or Tumor Development

Other than adverse events of Skin papilloma, no neoplasms were reported in the NDA submission.

8.7.2. Human Reproduction and Pregnancy

Not applicable. Subjects were boys between the ages of 5 to 16.

8.7.3. Pediatrics and Assessment of Effects on Growth

In placebo-controlled studies, changes in height, weight, and body mass index were similar in drisapersen 6 mg/kg/week and placebo subjects in up to 1 year of treatment.[140]

8.7.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose

There were no adverse events of overdose in the clinical program.

Drug abuse potential

In a consult regarding NDA 206031, the FDA Controlled Substance Staff found no issues related to drug abuse potential and provided the following conclusions:

> "1. No oligonucleotide is scheduled under the Controlled Substance Act and we are unaware of any instance(s) of abuse for oligonucleotides as a therapeutic class.
> 2. Drisapersen did not show any neurobehavioral changes in pre-clinical tests (Irwin test) and we are unaware of any pharmacological interaction with known CNS receptors of abuse (opioid, dopamine, etc). *Accordingly, the Sponsor's proposed label does not include a Section 9 (Abuse and Dependence).*
> 3. Drisapersen has no structural similarities between the chemical structure known drugs or abuse such as amphetamine, cocaine, benzodiazepines, opioids, LSD, MDMA, PCP, and cannabinoid agonists.
> 4. Drisapersen is not a prodrug of a known drug of abuse."

[140] Table 11.72 on ISS p. 3033-3037.

Reviewer comment: This reviewer agrees with the Controlled Substance Staff conclusions.

Withdrawal and rebound

This reviewer preformed a search using the MedDRA Drug Withdrawal SMQ. No drug withdrawal or rebound adverse events were found in drisapersen clinical studies.

8.8. Safety in the Postmarket Setting

8.8.1. Safety Concerns Identified Through Postmarket Experience

Not applicable. There is no previous postmarket experience.

8.8.2. Expectations on Safety in the Postmarket Setting

The clinical study findings may not fully represent drisapersen clinical safety in the setting of more advanced DMD. All studies [except for open label study PRO051-02 (N=12)] included only ambulant subjects. Also, the pharmacokinetics of drisapersen may be different in the non-ambulant population, because of differences in muscle mass.

If it is approved, drisapersen will be administered by a health professional, in a way similar to administration in clinical studies. Because its mechanism of action is specific to the treatment of Duchenne muscular dystrophy (DMD) with mutations in the dystrophin gene that are amenable to treatment with exon 51 skipping, we do not anticipate significant off-label use of drisapersen.

8.9. Additional Safety Issues From Other Disciplines

The reader is referred to Section 4 of this review.

8.10. Integrated Assessment of Safety

The main safety concerns with drisapersen are drug-induced immune thrombocytopenia, renal toxicity, and injection site reactions, and inflammation. Hepatic accumulation is a class effect and hepatic adverse events occurred in the clinical trials.

Six drisapersen subjects (2%) had thrombocytopenia <20 x 10^9/L, levels at which patients are at risk potentially fatal complications, including spontaneous intracranial or intrapulmonary hemorrhage. Most of these patients had confirmed anti-platelet antibodies. These cases occurred 14-26 months after the first dose of drisapersen. Platelet monitoring every 2 weeks, patient education regarding the signs and symptoms of thrombocytopenia, and facilitating prompt medical assessment and treatment can mitigate the risk of clinically significant

bleeding. Concomitant use of drisapersen with antiplatelet, thrombolytic, or anticoagulant drugs is not recommended. Patients taking these drugs were excluded from clinical studies.

Renal toxicity was reported in 61% of drisapersen 6 mg/kg/week subjects, compared to 34% of placebo subjects. Proteinuria was the most common renal toxicity reported in 44% of drisapersen 6 mg/kg/week subjects compared to 23% of placebo subjects. One drisapersen subject developed multiple life-threatening thromboses with bilateral pulmonary emboli in the setting of glomerulonephritis with nephrotic syndrome. Renal laboratory monitoring every 2 weeks and cessation of drisapersen according to recommended laboratory criteria can mitigate the risk of glomerulonephritis.

Injection site reactions including discoloration, induration, pain, pruritus, bruising, atrophy, hematoma, and swelling, occurred in 79% of drisapersen patients. The risk for first injection site reaction occurred throughout the first 72 weeks of exposure. 21% of reactions were not resolved by the end of the studies. Reactions known to resolve lasted for a mean of 58 days and up to 1217 days. Injection site reactions occurred despite administration by a medical professional and rotation of injection sites. No other strategies to mitigate the risk of injection site reactions are known.

In nonclinical studies, inflammatory effects of drisapersen were evident in mice and monkeys, impacting a multitude of organs and tissues and implicated in the majority of premature sacrifices or deaths. In clinical studies, larger changes in inflammatory markers MCP-1, complement C3, and hsCRP occurred in drisapersen subjects, compared to placebo. Serious adverse events in drisapersen subjects had or may have had an inflammatory etiology included myocardial ischemia, intracranial venous sinus thrombosis, and small intestinal obstruction with inflammatory changes. Describing preclinical and clinical inflammation findings in the product label will educate prescribers about this issue. If a patient has inflammatory changes after drisapersen treatment, withholding treatment may be considered if the risk outweighs the benefit.

Phosphorothioate oligonucleotides are known to accumulate in the liver, and hepatic toxicity AEs occurred in 10.5% subjects treated with drisapersen 6 mg/kg/week. Monitoring of liver function tests, including GGT, bilirubin, and INR, monthly will mitigate the risk of hepatic toxicity.

I recommend a patient registry as a post-marketing requirement to evaluate the main safety risks of drisapersen in the post-marketing setting. I recommend a boxed warning with recommendations for monitoring and administration to mitigate the risks of renal adverse events, thrombocytopenia, and injection site reactions and I recommend a Medication Guide to educate patients about these risks.

9 Advisory Committee Meeting and Other External Consultations

An advisory committee meeting is scheduled. At the time of this review, it has not yet been held.

10 Labeling Recommendations

10.1. Prescribing Information

This reviewer recommends a boxed warning to describe the thrombocytopenia, renal toxicity, and injection site reactions with drisapersen. Recommendations for laboratory monitoring will be necessary for thrombocytopenia, renal toxicity, and hepatic toxicity. This reviewer also recommends a Medication Guide (see Section 10.2).

10.2. Patient Labeling

This reviewer recommends development of a Medication Guide. It will be an important tool in educating patients and caregivers about the symptoms of severe thrombocytopenia (e.g., petechiae, bruising, bleeding) to facilitate prompt recognition and treatment.

10.3. Non-Prescription Labeling

Not applicable.

11 Risk Evaluation and Mitigation Strategies (REMS)

11.1. Safety Issue(s) that Warrant Consideration of a REMS

Safety issues that warrant consideration of a REMS include:

- Thrombocytopenia
- Renal toxicity
- Injection site reactions

11.2. Conditions of Use to Address Safety Issue(s)

Conditions of use to address the safety issues listed in Section 11.1 are described below.

Thrombocytopenia

Laboratory monitoring every 2 weeks will be necessary to mitigate the risk of complications related to thrombocytopenia with drisapersen. Patients would see a medical professional

weekly for administration of drisapersen. This weekly contact with a medical professional will facilitate laboratory monitoring.

Educating patients and caregivers about the symptoms of severe thrombocytopenia (e.g., petechiae, bruising, bleeding) will be necessary to mitigate the risk of complications related to thrombocytopenia with drisapersen. A Medication Guide can be used as an education tool.

Renal toxicity

Quantitative urine testing every 2 weeks will be necessary to mitigate the risks of renal toxicity with drisapersen. With abnormal results, weekly quantitative urine testing may be necessary. Patients would see a medical professional weekly for administration of drisapersen. This weekly contact with a medical professional will facilitate quantitative urine testing.

Injection Site Reactions

Proper administration technique and knowledge about injection site reactions caused by drisapersen are necessary for safe use. Patients would see a medical professional weekly for administration of drisapersen, which will facilitate risk mitigation.

11.3. Recommendations on REMS

At the time of this review, the Division of Neurology Products and the Division of Risk Management (DRISK) in the Office of Surveillance and Epidemiology do not recommend a REMS for this NDA. Factors influencing this decision include:

- Duchenne muscular dystrophy (DMD) is mainly treated in specialty centers with detailed knowledge of DMD and its treatment.
- Patients would see a medical professional weekly for administration of drisapersen, which will facilitate risk mitigation.
- The DMD community is active in educating patients and families regarding DMD treatment.

12 Postmarketing Requirements and Commitments

I recommend a patient registry as a post-marketing requirement to evaluate the main safety risks of drisapersen in the post-marketing setting.

13 Appendices

13.1. References

References are included as footnotes throughout this review document.

13.2. Financial Disclosure

The reader is referred to the review of clinical efficacy by Dr. Veneeta Tandon.

13.3. Frequency of laboratory measurements

Phase I/II Studies								
Phase I/II Studies								
PRO051-02 - 5 escalating doses) (Study duration of 18 weeks (up to Visit 12)								
Parameter	Screening	Day of dosing	+ 1 day (+24 hrs)	+ 7 days	+ 14 days	+21 days	+ 28 days (1 Mth)	Follow-up (no treatment)
Haematology	S1 + S2	X (pre-dose t=-3 to 0)		X (pre-dose t=-3 to 0 and +24±3 hrs post-dose)	X pre-dose t=-3 to 0 and +24±3 hrs post-dose)	X pre-dose t=-3 to 0 and +24±3 hrs post-dose)	X (pre-dose t=-3 to 0 and +24±3 hrs post-dose)	+ 1 week, + 1 week, +3 weeks and + 3 weeks
Biochemistry	S1 + S2	X (pre-dose t=-3 to 0)						
Urinalysis	X	X (pre-dose t=-3 to 0)						
aPTT		X (pre-dose t=-3 to 0)	X (+3hrs, +6hrs, +24hr post-dose)				X (t=-3 to 0 pre-dose, + 3 hrs, + 6 hrs, +24 hrs post-dose)	
Complement split products		X (pre-dose t=-3 to 0)	X (+3hrs, +6hrs, +24hr post-dose)					
Inflammatory markers		X (pre-dose t=-3 to 0)	X (+3hrs, +6hrs, +24hr post-dose)					
Dystrophin AB		X (pre-dose t=-3 to 0)						+6 weeks and + 4 weeks

Haematology Parameters: haemoglobin, MCV, erythrocyte count, haematocrit, MCH, MCHC, reticulocyte count, thrombocyte count, leukocyte count, leukocyte differentiation (neutrophils, eosinophils, basophils, monocytes, lymphocytes)
Biochemistry Parameters: sodium, potassium, calcium, BUN, creatinine, AST, ALT, GGT, LDH, alkaline phosphatase, bilirubin, CK, amylase, total protein, albumin, glucose, cholesterol, fatty acids (only for original protocol and Amendment 1)
Urinalysis (dipstick): leukocytes, blood, protein, ketones, glucose, nitrite, pH, urine sediment, protein electrophoresis. Quantitative urinalysis (urine protein to creatinine ratio): protein, creatinine
Complement Factors: complement factor C3, complement split products (C3a, SC5b-9, Bb)
Inflammatory Factors:IL-6, TNF-α, MCP-1
HIV/HBV/HCV will be performed at screening visit
Abbreviations: AB = Antibodies, aPTT = Activated Partial Thromboplastin Time, t = time

DMD114673 (extension study of PRO051-02 - weekly dosing for 72 weeks, intermittent dosing[a] for 96 weeks with a sub-group testing IV dosing)	
Parameter	Frequency
Haematology (excl Thrombocyte count)	every 4 weeks for 40 weeks, +8 weeks, every 4 weeks for 40 weeks, 9 cycles of +5 weeks, +3 weeks, +4 weeks + 5 weeks (IV dosing subset only: pre-dose and +24 hrs post-dose, followed by 4 cycles of +1 week, +2 weeks (IV dosing subset only: pre-dose and +24hrs post-dose) + 1 week, + 2 weeks, + 4 weeks, + 5 weeks, + 3 weeks
Biochemistry	every 4 weeks for 40 weeks, +8 weeks, every 4 weeks for 40 weeks, 9 cycles of +5 weeks, +3 weeks, +4 weeks + 5 weeks (IV dosing subset only: pre-dose and +24 hrs post-dose, followed by 4 cycles of +1 week, +2 weeks (IV dosing subset only: pre-dose and +24hrs post-dose)
Thrombocyte Count	every 2 weeks (for when study drug is administered)
Urinalysis	weekly for 16 weeks and every 2 weeks for 20 weeks, + 4 weeks, + 8 weeks, + 4 weeks for 20 weeks, + 4 weeks, + 4 weeks, + 2

Phase I/II Studies	
	weeks (for 8 weeks), 8 cycles of + 5 weeks, +1 week, + 2 weeks + 2 weeks, + 2 weeks, + 5 weeks (IV dosing subset only: pre-dose and +24 hrs post-dose and metabolite recovery from 0-24 hours) and 4 cycles of +1 week, + 2 weeks (IV dosing subset only: pre-dose and +24 hrs post-dose and metabolite recovery from 0-24 hours), + 1 week, + 2 weeks (for 6 weeks), + 5 weeks, + 1 week, + 2 weeks
Urine α1-microglobulin	every 12 weeks for 48 weeks, every 4 weeks for 40 weeks, intermittent dosing schedule cycle: + 5 weeks, +3 weeks, + 4 weeks (for 96 weeks), + 5 weeks (IV dosing subset only: pre-dose and +24 hrs post-dose) and 4 cycles of +1 week, + 2 weeks (IV dosing subset only: pre-dose and +24 hrs post-dose),+ 1 week, +2 weeks, + 4 weeks, + 5 weeks, + 3 weeks
Urine cystatin C	every 4 weeks for 20 weeks (starting from Week 68), intermittent dosing schedule cycle: + 5 weeks, +3 weeks, + 4 weeks (for 96 weeks), + 5 weeks (IV dosing subset only: pre-dose and +24 hrs post-dose) and 4 cycles of +1 week, + 2 weeks (IV dosing subset only: pre-dose and +24 hrs post-dose), + 1 week, +2 weeks, + 4 weeks, + 5 weeks, + 3 weeks
Complement split products	every 4 weeks for 88 weeks, intermittent dosing schedule cycle: + 5 weeks, +3 weeks, + 4 weeks (for 96 weeks), + 5 weeks (IV dosing subset only: pre-dose, + 2 hours, + 4 hours, + 6 hours, +24 hrs post-dose) and 4 cycles of +1 week, + 2 weeks (IV dosing subset only: pre-dose, + 2 hours, + 4 hours, + 6 hours, +24 hrs post-dose)+ 1 week, +2 weeks, + 4 weeks, + 5 weeks, + 3 weeks
Troponin	every 4 weeks for 56 weeks only
Fibrinogen	every 4 weeks for 88 weeks, intermittent dosing schedule cycle: + 5 weeks, +3 weeks, + 4 weeks (for 96 weeks), + 5 weeks (IV dosing subset only: pre-dose and +24 hrs post-dose, followed by 4 cycles of +1 week, +2 weeks (IV dosing subset only: pre-dose and +24hrs post-dose) , + 1 week, +2 weeks, + 4 weeks, + 5 weeks, + 3 weeks
Haptoglobin	every 4 weeks for 88 weeks, intermittent dosing schedule cycle: + 5 weeks, +3 weeks, + 4 weeks (for 96 weeks), + 5 weeks (IV dosing subset only: pre-dose and +24 hrs post-dose, followed by 4 cycles of +1 week, +2 weeks (IV dosing subset only: pre-dose and +24hrs post-dose), +1 week, +2 weeks, + 4 weeks, + 5 weeks, + 3 weeks
C-Reactive Protein	every 4 weeks for 88 weeks, intermittent dosing schedule cycle: + 5 weeks, +3 weeks, + 4 weeks (for 96 weeks), + 5 weeks (IV dosing subset only: pre-dose, + 2 hours, + 4 hours, + 6 hours, +24 hrs post-dose) and 4 cycles of +1 week, + 2 weeks (IV dosing subset only: pre-dose, + 2 hours, + 4 hours, + 6 hours, +24 hrs post-dose), +1 week, +2 weeks, + 4 weeks, + 5 weeks, + 3 weeks
Inflammatory markers (IL-6, TNF-α, MCP-1)	MCP-1 as per biochemistry schedule IL-6/TNF-α - IV dosing subset only: pre-dose, + 2 hours, + 4 hours, + 6 hours, +24 hrs post-dose
Cystatin C	every 12 weeks for 96 weeks, 7 cycles of +4 weeks, + 5 weeks, + 3 weeks, then + 4 weeks, IV dosing: pre-dose and +24 hrs, followed by 4 cycles of +1 week, +2 weeks (pre-dose and +24hrs post-dose), +1 week, , + 2 weeks, + 4 weeks, + 5 weeks, + 3 weeks
Coagulation Parameters (blood)	every 4 weeks for 88 weeks, intermittent dosing schedule cycle: + 5 weeks, +3 weeks, + 4 weeks (for 96 weeks), + 5 weeks (IV dosing subset only: pre-dose, + 2 hours, + 4 hours, + 6 hours, +24 hrs post-dose) and 4 cycles of +1 week, + 2 weeks (IV dosing subset only: pre-dose, + 2 hours, + 4 hours, + 6 hours, +24 hrs post-dose),+ 1 week, +2 weeks, + 4 weeks, + 5 weeks, + 3 weeks
Dystrophin AB	every 12 weeks for 24 week and then every 24 weeks thereafter

a. Intermittent dosing = 8 weeks of weekly treatment, 4 weeks off treatment (1 cycle)
Haematology: haemoglobin, haematocrit, MCV, MCH, MCHC, erythrocyte count, reticulocyte count, leukocyte count, leukocyte differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes), thrombocyte count, blood smear for schistocytes
Biochemistry Parameters: sodium, potassium, calcium, BUN, creatinine, creatinine clearance (calculated), cystatin C, AST, ALT, GGT, LDH, GLDH, alkaline phosphatase, bilirubin, amylases, CK, total protein, albumin, albumin/globulin ratio, glucose, cholesterol, cystatin C, MCP-1
Urinalysis: glucose, albumin, protein, creatinine, KIM-1, protein/creatinine ratio, microscopy of urine sediment for erythrocytes, leukocytes and casts, protein electrophoresis
Coagulation Parameters (blood): aPTT, PTT (INR)
HIV/HBV/HCV will be performed at screening visit

Phase I/II Studies			
Phase II Studies			
Parameter	Screening	Day of First Dose	Frequency
DMD114117 (48 Weeks Treatment Duration)			
Haematology (excl Thrombocyte count)	S1 + S2	X (pre-dose)	+2 weeks, + 2 weeks and every 4 weeks up to Week 25, and every 8 weeks thereafter (all samples pre-dose)
Biochemistry	S1 + S2	X (pre-dose)	+2 weeks, + 2 weeks and every 4 weeks up to Week 25, and every 8 weeks thereafter (all samples pre-dose)
Thrombocyte Count	S1 + S2	X (pre-dose)	Required every 2 weeks (all samples pre-dose)
Urinalysis	S1 + S2	X (pre-dose)	Every 2 weeks (all samples pre-dose)
24-hour Urine		X (pre-dose)	To be performed if stopping criteria met
Dystrophin AB		X (pre-dose)	+12 weeks, + 8 weeks, + 12 weeks (all samples pre-dose)
Coagulation Parameters	S1 + S2	X (pre-dose)	+2 weeks, + 2 weeks and every 4 weeks up to Week 25, and every 8 weeks thereafter (all samples pre-dose)
Renal Markers (α1-microglobulin/Cystatin C/KIM-1)	S1	X (pre-dose)	Every 4 weeks (all samples pre-dose)
Haematology: haemoglobin, haematocrit, MCV, MCH, MCHC, erythrocyte count, reticulocyte count, leukocyte count, leukocyte differential count (bands forms, segment forms, neutrophils, eosinophils, basophils, monocytes, lymphocytes), blood smear for schistocytes, Biochemistry Parameters: sodium, potassium, calcium, phosphate, BUN, creatinine, creatinine clearance, cystatin C, AST, ALT, GGT, LDH, GLDH, alkaline phosphatase, bilirubin (total), bilirubin (conjugated or "direct"), CK, total protein, albumin, albumin/globulin ratio, glucose, complement factor C3, haptoglobin, fibrinogen, CRP, IgG, Dystrophin antibodies, monocyte chemotactic protein-1 (MCP-1) Urinalysis (morning spot urine): glucose, albumin, protein, creatinine, protein/creatinine ratio, microscopy of urine sediment for erythrocytes, leukocytes and casts, protein electrophoresis Coagulation Parameters (blood): aPTT, PTT (INR) HIV/HBV/HCV will be performed at screening visit 1 Abbreviations: AB = Antibodies, KIM-1 = Kidney Injury Molecule 1, S = Screening, W = Week, HIV = Human Immunodeficiency Virus, HBV = Hepatitis B Virus, HCV = Hepatitis C Virus			
DMD114876 (24 Weeks Treatment Duration and 24 Weeks Follow-up)			
Haematology (excl Thrombocyte count)	S1	X (pre-dose)	+2 weeks, + 2 weeks, + 4 weeks and every 4 weeks until Week 24 then +6 until week 36, then + 12 weeks (all samples pre-dose)
Biochemistry	S1	X (pre-dose)	+2 weeks, + 2 weeks, + 4 weeks and every 4 weeks until Week 24, then +6 weeks until week 36, then + 12 weeks (all samples pre-dose)
Thrombocyte Count	S1	X (pre-dose)	Required every 2 weeks (all samples pre-dose)
Urinalysis	S1	X (pre-dose)	Every 2 weeks for 30 weeks + 18 weeks (all samples pre-dose)
24-hour Urine	S1 or S2		
Dystrophin AB		X (pre-dose)	+12 weeks and + 12 weeks (all samples pre-dose)
Fibrin Split Products, D-dimer and Schistocytes	S1	X (pre-dose)	every 4 weeks until Week 24 (all samples pre-dose)
Coagulation Parameters	S1	X (pre-dose)	+2 weeks, + 2 weeks, + 4 weeks and every 4 weeks until Week 24 then +6 until week 36, then + 12 weeks (all samples pre-dose)
Haematology: haemoglobin, haematocrit, MCV, MCH, MCHC, erythrocyte count, reticulocyte count, leukocyte count, leukocyte differential count (bands forms, segment forms, neutrophils,			

Phase I/II Studies

eosinophils, basophils, monocytes, lymphocytes)
Biochemistry Parameters: sodium, potassium, calcium, phosphate, BUN, creatinine, creatinine clearance (calculated), cystatin C, AST, ALT, GGT, LDH, GLDH, alkaline phosphatase, bilirubin (total), bilirubin (conjugated or "direct"), CK, total protein, albumin, globulin, albumin/globulin ratio, glucose, complement factor C3, haptoglobin, fibrinogen, hsCRP, IgG, Dystrophin antibodies, MCP-1
Urinalysis (morning spot urine): glucose, albumin, protein, creatinine, α1-microglobulin, protein/creatinine ratio, urine cystatin C, KIM-1, microscopy of urine sediment for erythrocytes, leukocytes and casts
Urinalysis (24-hour urine): protein, albumin, creatinine (urine and serum), protein electrophoresis
Coagulation Parameters (blood): aPTT, PTT (INR)
HIV/HBV/HCV will be performed at screening visit
Abbreviations: AB = Antibodies, KIM-1 = Kidney Injury Molecule 1, S = Screening, W = Week

Phase III Study

Parameter	Screening	Day of First Dose	Frequency
DMD114044 (48 Weeks Treatment Duration)			
Haematology (excl Thrombocyte count)	S1	X (pre-dose)	+2 weeks, + 2 weeks, and every 4 weeks (all samples pre-dose)
Biochemistry	S1	X (pre-dose)	+2 weeks, + 2 weeks, and every 4 weeks (all samples pre-dose)
Thrombocyte Count	S1	X (pre-dose)	Required every 2 weeks (all samples pre-dose)
Urinalysis	S1	X (pre-dose)	Every 2 weeks (all samples pre-dose)
24-hour Urine	X (prior to randomisation)		To be performed if stopping criteria met
Coagulation Parameters	S1	X (pre-dose)	+2 weeks, + 2 weeks, and every 4 weeks (all samples pre-dose)
Dystrophin AB		X (at randomisation)	every 12 weeks (all samples pre-dose)

Haematology: haemoglobin, haematocrit, MCV, MCH, MCHC, erythrocyte count, reticulocyte count, leukocyte count, leukocyte differential count (bands forms, segment forms, neutrophils, eosinophils, basophils, monocytes, lymphocytes), blood smear for schistocytes
Biochemistry Parameters: sodium, potassium, calcium, phosphate, BUN, creatinine, creatinine clearance (calculated), cystatin C, AST, ALT, GGT, LDH, GLDH, alkaline phosphatase, bilirubin (total), bilirubin (conjugated or "direct"), CK, total protein, albumin, globulin, albumin/globulin ratio, glucose (fasting), complement factor C3, haptoglobin, fibrinogen, CRP, IgG, Dystrophin antibodies, MCP-1
Urinalysis: glucose, albumin, protein, creatinine, α1-microglobulin, protein/creatinine ratio, urine cystatin C, KIM-1, microscopy of urine sediment for erythrocytes, leukocytes and casts, protein electrophoresis
Coagulation Parameters (blood): aPTT, PTT (INR)
HIV/HBV/HCV will be performed at screening visit
Abbreviations: S = Screening, W = Week

Phase I/II Studies		
Extension Phase Study		
Parameter	Day of First Dose	Frequency
DMD114349 (104 Weeks Treatment Duration and 20 Weeks Follow-up)		
Haematology (excl Thrombocyte count)	X (pre-dose)	+2 weeks, + 2 weeks, and every 4 weeks up to Week 24 and 8 weekly thereafter (all samples pre-dose)
Biochemistry	X (pre-dose)	+2 weeks, + 2 weeks, and every 4 weeks up to Week 24 and 8 weekly thereafter (all samples pre-dose)
Thrombocyte Count	X (pre-dose)	Required every 2 weeks (all samples pre-dose)
Urinalysis	X (pre-dose)	Every 2 weeks (all samples pre-dose)
Coagulation Parameters	X (pre-dose)	+2 weeks, + 2 weeks, and every 4 weeks up to Week 24 and 8 weekly thereafter (all samples pre-dose)
Dystrophin AB	X (pre-dose)	+12 weeks (removed in Amendment 1), + 12 weeks (all samples pre-dose)
Haematology: haemoglobin, haematocrit, MCV, MCH, MCHC, erythrocyte count, reticulocyte count, leukocyte count, leukocyte differential count (bands forms, segment forms, neutrophils, eosinophils, basophils, monocytes, lymphocytes), blood smear for schistocytes Biochemistry Parameters: sodium, potassium, calcium, phosphate, BUN, creatinine, creatinine clearance (calculated), cystatin C, AST, ALT, GGT, LDH, alkaline phosphatase, bilirubin (total), bilirubin (conjugated or "direct"), CK, total protein, albumin, albumin/globulin ratio, glucose, complement factor C3, haptoglobin, fibrinogen, CRP, MCP-1 Urinalysis (morning spot urine): glucose, albumin, protein, creatinine, protein/creatinine ratio, microscopy of urine sediment for erythrocytes, leukocytes and casts. Urinalysis (24-hour urine): protein, albumin, creatinine (urine and serum), protein electrophoresis Coagulation Parameters (blood): aPTT, PTT (INR) HIV/HBV/HCV will be performed at screening visit Abbreviations: W = Week		

Source: P. 223-227 Summary of Clinical Safety.

V. Statistical Review

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

sNDA/BLA Serial Number:	206,031
Drug Name:	Drisapersen
Indication(s):	Duchenne Muscular Dystrophy
Applicant:	Biomarin
Date(s):	Date of Submission: April 27, 2015 PDUFA Due Date: December 27, 2015
Review Priority:	Priority Review
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	Sharon Yan, Ph.D.
Concurring Reviewers:	Kun Jin, Ph.D., Team Leader James Hung, Ph.D., Director
Medical Division:	Neurology
Clinical Team:	Veneeta Tandon, M.D., Clinical Reviewer Evelyn Mentari, M.D., Safety Reviewer Ronald Farkas, M.D., Team Leader Eric Bastings, M.D., Deputy Director Billy Dunn, M.D., Director
Project Manager:	Fannie Choy, RPh.

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1 EXECUTIVE SUMMARY

The submission of this NDA contains one phase-3 study (DMD114044) and two phase-2 studies (DMD114117 and DMD114876). All three studies were randomized, double-blind, parallel-group studies in ambulant subjects with Duchenne muscular dystrophy (DMD) resulting from a mutation thought to be corrected by exon 51 skipping induced by drisapersen.

The phase-2 study DMD114117, with 53 randomized patients, included 4 treatment arms of 6 mg/kg drisapersen continuous regimen, 6 mg/kg drisapersen intermittent regimen, placebo continuous regimen and placebo intermittent regimen. The treatment of 6 mg/kg drisapersen continuous regimen met the primary objective by showing an adjusted mean improvement of 35 meters over 24 weeks in 6-minute walking distance (6MWD) test compared to combined placebo group (p=0.014). No treatment benefit was observed for the 6 mg/kg drisapersen intermittent regimen.

The phase-2 study DMD114876, with 51 randomized patients, included 4 treatment arms of 3 mg/kg drisapersen, 6 mg/kg drisapersen, and volume matched 3 mg/kg placebo and 6 mg/kg placebo. Neither of the drisapersen doses achieved statistically significant treatment effect. A numerical difference of 27 meters (p=0.069) in favor of 6 mg/kg drisapersen compared to combined placebo was observed.

The large phase-3 study DMD114044 conducted concurrently with a total of 186 randomized patients failed to demonstrate treatment benefit of drisapersen 6 mg/kg over placebo. The adjusted mean treatment difference of 10 meters carried a p-value of 0.415.

Differences among the 3 studies, mainly between the phase-2 and phase-3 studies in demographic and baseline characteristics, were observed. Patients enrolled in the phase-2 studies were relatively younger and less impaired with higher baseline 6MWD scores compared to the phase-3 study.

2 INTRODUCTION

2.1 Overview

DMD is a severe, progressive fatal pediatric neuromuscular disorder for which there is no available therapy. It occurs almost exclusively in males.

Drisapersen was studied under IND 105284 and was granted Orphan Drug Designation, Fast Track designation, and breakthrough therapy designation.

The submission of this NDA included 3 clinical studies: DMD114044, DMD114117, and DMD114876, referred as studies 044, 117 and 876 thereafter. Study 044 was a phase-3 study and studies 117 and 876 were phase-2 studies. All three studies were randomized, double-blind, parallel-

group studies in ambulant subjects with Duchenne muscular dystrophy (DMD) resulting from a mutation thought to be corrected by exon 51 skipping induced by drisapersen.
In Study 044, subjects were randomized to receive either drisapersen 6 mg/kg or dose-matched placebo (2:1 ratio) as subcutaneous injections once a week for 48 weeks. A total of 186 patients were randomized: 125 patients to the 6 mg/kg drisapersen group and 61 patients to the placebo group. The study endpoint was change from baseline in 6-minute walking distance (6MWD) test. No statistically significant treatment difference was found (p=0.415).

Study 117 included 2 drisapersen regimens, a 6 mg/kg continuous regimen and a 6 mg/kg intermittent regimen. A total of 53 patients were randomized. Patients were treated for 48 weeks, but the efficacy was evaluated at week 24. The same study endpoint as in Study 044 was used. A statistically significant (p=0.014) treatment benefit of 35 meters in the change from baseline in 6MWD was observed for the 6 mg/kg drisapersen continuous regimen compared to placebo. No treatment benefit was observed for the 6 mg/kg intermittent regimen.

Study 876 included a 3 mg/kg drisapersen dose group, a 6 mg/kg drisapersen dose group and dose volume matched placebo groups. A total of 51 patients were randomized in the 4 treatment groups. Patients were treated for 24 weeks. A numerical treatment difference of 27 meters in the change from baseline in 6MWD favoring 6 mg/kg drisapersen did not achieve statistical significance (p=0.069). The 3 mg/kg drisapersen dose did not show treatment benefit.

A summary of the phase-2 and phase-3 studies included in this review is presented in Table 1.

Table 1 List of studies included in this review

Study	Phase and Design	Duration of treatment	Dosage/ regiment	Comparator	# of Subjects randomized
Protocol 114044	Phase 3, randomized, double-blind, PBO-controlled	48 weeks	6 mg/kg/wk	Placebo	186
Protocol 114117	Phase 2, randomized, double-blind, PBO-controlled	48 weeks	6 mg/kg/wk continuous & 6 mg/kg/wk intermittent	Placebo	53
Protocol 114876	Phase 2, randomized, double-blind, PBO-controlled	24 weeks	6 mg/kg/wk & 3 mg/kg/wk	Placebo	51

2.2 Data Sources

All documents reviewed for this NDA submission are in electronic form with eCTD format. The electronic files are compatible with eCTD viewer software Global Summit. Both raw and derived datasets are included in the submission. The SAS programs for primary and secondary analyses

are also included. The path to CDER Electronic Document Room for documents of this NDA is listed below:
\\cdsesub1\evsprod\NDA206031

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

No issues in data and analysis quality were identified.

3.2 Evaluation of Efficacy

3.2.1 Evaluation of Study 044

3.2.1.1 Study Design – Study 044

The primary objective of Study 044 was to assess the efficacy of subcutaneous 6 mg/kg drisapersen versus placebo administered weekly over 48 weeks in ambulant subjects with DMD.

Study 044 was a phase 3, randomized, double-blind, parallel-group study in ambulant subjects with DMD resulting from a mutation thought to be corrected by exon 51 skipping induced by drisapersen. The study enrolled male patients with minimum age of 5 years.

Prior to randomization, subjects had two screening visits, one at 2~4 weeks prior to the first dose and one at 1~2 weeks prior to the first dose. The 6MWD test was performed at both screening visits as well as randomization/baseline visit. Subjects had to be able to complete 6MWD test with minimal distance of 75 meters at each pre-drug visit. In addition, results of 6MWD had to be within 20% of each other at each pre-drug visit.

Subjects were randomized to receive either drisapersen 6 mg/kg or dose-matched placebo (2:1 ratio) as subcutaneous injections once a week for 48 weeks. At the end of the treatment period, subjects who completed the study had the option to enter into an open-label extension study (Study DMD114349).

Study 044 was conducted in 44 centers in 19 countries. A schematic of the study design is presented in Figure 1.

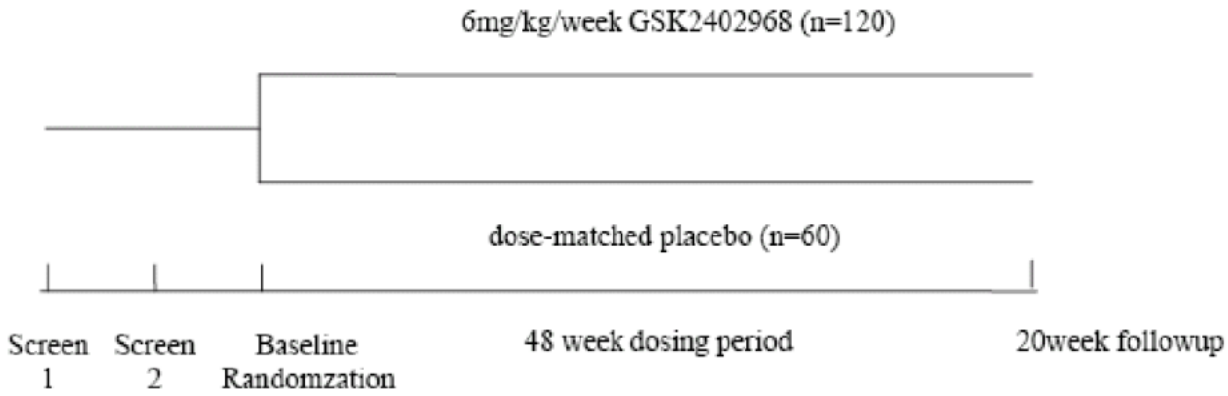

Figure 1 Study Schematic
Source: Clinical Study Report

3.2.1.2 Study Endpoints – Study 044

The primary efficacy endpoint was muscle function using 6-minute walking distance (6MWD) test assessed at Week 48.

During the 6MWD, subjects were asked to walk, at their own preferred speed, up and down a fixed distance until they were told to stop after 6 minutes. The subjects were warned of the time and were told that they could stop earlier if they felt unable to continue. The total distance walked within 6 minutes (or until the subject stopped in case of early termination of the test) was recorded in meters; any falls were also recorded.

The 6MWD was conducted at Screen 1, Screen 2, Baseline (Week 1), Weeks 12, 24, 36 and 48 or Early Withdrawal.

Key secondary endpoints (rank ordered) were:

- Change from baseline in Linearized North Star Ambulatory Assessment (NSAA) total score
- Change from baseline in 4-stair climb (ascent) velocity
- Change from baseline in the 10-meter walk/run velocity

3.2.1.3 Statistical Methodologies – Study 044

The primary population for efficacy evaluation was the ITT population, which was defined as all subjects who were randomized to the study, received at least one dose of study medication and had at least one post-baseline efficacy assessment.

Change from baseline in the 6MWD was analyzed on all available assessment data from the ITT population using a mixed model for repeated measures (MMRM) with restricted maximum likelihood estimation and an unstructured covariance matrix. The MMRM model included fixed

categorical terms for treatment, visit, treatment-by-visit interaction, country grouping, and continuous fixed covariates of baseline 6MWD and baseline 6MWD-by-visit interaction.

The primary time point of interest was the end of treatment (Week 48). Additional supportive analyses for treatment differences for Weeks 12, 24 and 36 were also estimated using the MMRM model.

If the assumptions of normality were not met, a log-transformation of the data prior to an MMRM analysis, or non-parametric analysis producing Hodges-Lehmann estimates of the Wilcoxon Rank Sum Test were to be provided. The primary inference was to be based on the MMRM models.

The following sensitivity analyses were to be performed to examine the robustness of the results in the presence of missing data, and to determine the impact of protocol violators.
1. ANCOVA utilizing the data from all observed cases (OC) for the ITT population.
2. ANCOVA utilizing last-observation-carry-forward (LOCF) data, for the ITT population.
3. ANCOVA utilizing data imputed via multiple imputation, for the ITT population.
4. MMRM analysis utilizing available assessment data from the PP population.

The ANCOVA models included fixed terms for treatment group, baseline 6MWD, and country/center grouping.

Confirmatory statistical testing was to be performed only for the primary variable and key secondary endpoints through hierarchical testing in the given order.

Each secondary endpoint was analyzed for the OC dataset using a mixed model for repeated measures (MMRM). The MMRM model for each secondary endpoint included fixed terms for treatment, visit, treatment-by-visit interaction, country/country group, baseline score, and baseline score by visit.

The study aimed to randomize 180 subjects, assuming an approximate 10% dropout, in order to recruit at least 162 evaluable subjects. The study was designed to show superiority of drisapersen compared with dose-matched placebo with 90% power to detect a difference in 6MWD between drisapersen and placebo of 30 meters, assuming a common standard deviation of 55 meters.

3.2.1.4 Study Population Results – Study 044

3.2.1.4.1 Patient Disposition

A total of 186 subjects were randomized in 44 centers in 19 countries. A total of 5 subjects consisting of 1 (2%) subject in the placebo group and 4 (3%) subjects in the drisapersen group withdrew from the study prematurely (Table 2).

Table 2 Summary of Subject Disposition (Safety Population) – Study 044

Subject Status	Number (%) of Subjects		
	Placebo (N=61)	Drisapersen 6 mg/kg/week (N=125)	Total (N=186)
Completed	60 (98)	121 (97)	181 (97)
Withdrawn	1 (2)	4 (3)	5 (3)
Primary reason for study withdrawal[a]			
Adverse event[b]	0	2 (2)	2 (1)
Withdrew consent	0	2 (2)	2 (1)
Protocol deviation[c]	1 (2)	0	1 (<1)

Source: Clinical Study Report

3.2.1.4.2 Patient Demographic and Baseline Characteristics

Demographic characteristics were similar across treatment groups, though the drisapersen group had slightly higher percentage of patients in the older age group than the placebo group (Table 3).

Table 3 Summary of Demographic Characteristics (Safety Population) – Study 044

	Placebo (N=61)	Drisapersen 6 mg/kg/week (N-125)
Age (years)		
Mean (SD)	8.0 (2.37)	8.3 (2.43)
Median	8.0	8.0
$5 \leq$ age ≤ 7; n (%)	29 (47.5)	51 (40.8)
$7 <$ age ≤ 10; n (%)	25 (41.0)	53 (42.4)
Age > 10; n (%)	7 (11.5)	21 (16.8)
Sex, n (%)		
Male	61 (100)	125 (100)
Race, n (%)		
African American	1 (1.6)	0
Asian	9 (14.8)	20 (16.0)
White-Arabic/North African Heritage	4 (6.6)	5 (4.0)
White-Caucasian	46 (75.4)	95 (76.0)
Mixed	1 (1.6)	5 (4.0)

Source: Clinical Study Report

The time since first symptoms, diagnosis and first steroid use in the drisapersen group were numerically longer than the placebo group. The majority of subjects in both treatment groups (placebo: 85%; drisapersen: 86%) were on a continuous regimen of glucocorticosteroid. Mean baseline values for the 6MWD test were slightly lower in the drisapersen group (337.46 m) than in the placebo group (348.00 m). A summary of baseline disease characteristics is presented in Table 4.

Table 4 Summary of Baseline Disease Characteristics (Safety Population) – Study 044

	Placebo (N=61)	Drisapersen 6 mg/kg/week (N=125)	Total (N=186)
Time Since First Symptoms (months)[a]			
n	58	122	180
Mean (SD)	66.7 (31.30)	71.8 (31.58)	70.2 (31.49)
Median	60.8	70.2	66.8
Min., Max.	11, 168	12, 176	11, 176
Time Since Diagnosis (months)[a]			
n	61	125	186
Mean (SD)	54.2 (32.84)	58.0 (35.16)	56.7 (34.37)
Median	49.8	54.5	53.1
Min., Max.	6, 148	6, 163	6, 163
Time Since First Corticosteroid Taken (months)[a]			
n	61	125	186
Mean (SD)	29.1 (25.77)	35.6 (28.99)	33.5 (28.07)
Median	18.9	26.6	25.6
Min., Max.	7, 135	6, 146	6, 146
Corticosteroid Regimen, n (%)[b]			
n	61	125	186
Continuous	52 (85)	108 (86)	160 (86)
Intermittent	9 (15)	17 (14)	26 (14)
6MWD (m)	61	125	NA
Mean (SD)	348.00 (92.153)	337.46 (95.594)	NA

Source: Clinical Study Report

3.2.1.5 Efficacy Results – Study 044

Analysis of the Primary Endpoint

Mean decreases from baseline in 6MWD (m) were observed for both the placebo and drisapersen groups, indicating a decline in ambulatory function over 48 weeks. In the primary efficacy MMRM analysis of change from baseline in 6MWD (m) at Week 48 (Table 5 and Figure 2), a 10.3 m treatment difference over placebo was observed for the drisapersen treatment group. This difference was not statistically significant (p=0.415).

Table 5 Summary of MMRM Analysis of Change from Baseline in 6MWD (ITT Population) – Study 044

	Placebo (N=61)	Drisapersen 6 mg/kg/week (N=125)
Baseline		
n	61	125
Mean (SD)	348.00 (92.153)	337.46 (95.594)
Week 12		
n	58	124
Adjusted mean change (SE)	-12.80 (5.460)	-8.08 (3.877)
Adjusted mean difference vs. placebo		4.725
95% CI		(-8.081 ,17.530)
p-value		0.468
Week 24		
n	59	122
Adjusted mean change (SE)	-29.11 (8.267)	-24.34 (5.815)
Adjusted mean difference vs. placebo		4.767
95% CI		(-14.896, 24.431)
p-value		0.633
Week 36		
n	60	116
Adjusted mean change (SE)	-35.13 (9.010)	-33.24 (6.385)
Adjusted mean difference vs. placebo		1.887
95% CI		(-19.644, 23.419)
p-value		0.863
Week 48		
n	59	117
Adjusted mean change (SE)	-52.65 (10.423)	-42.32 (7.378)
Adjusted mean difference vs. placebo		10.334
95% CI		(-14.645, 35.312)
p-value		0.415

Source: Clinical Study Report

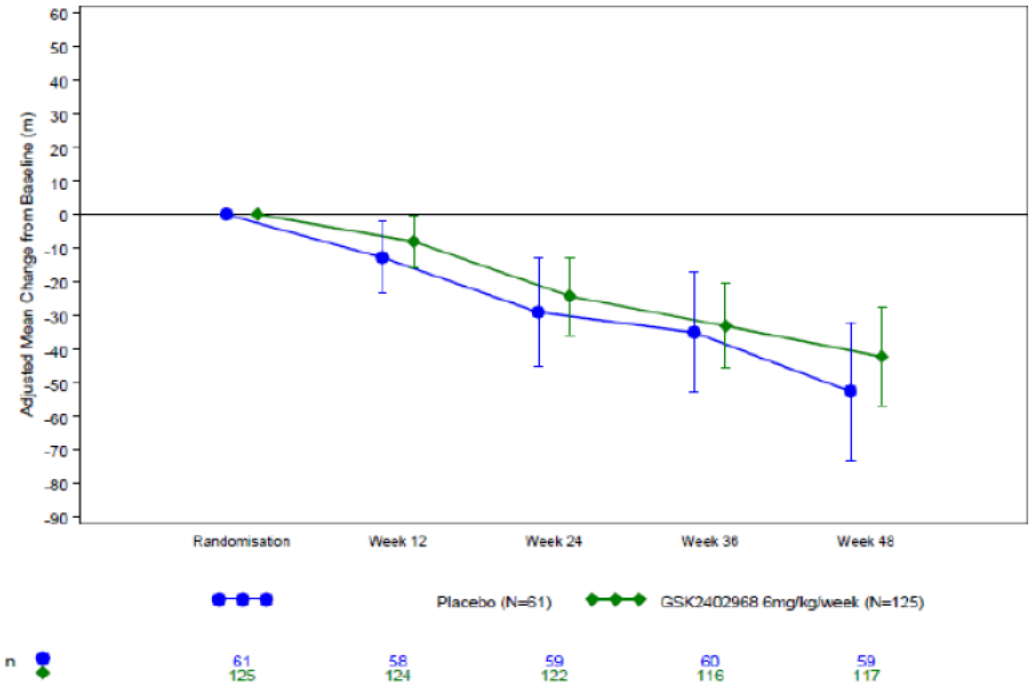

Figure 2 Adjusted Mean Change from Baseline (95% CI) in 6MWD (m) (ITT Population)
Source: Clinical Study Report

The planned sensitivity analyses (Section 3.2.1.3) were performed and the results were generally similar to the one obtained from the primary analysis (Table 6).

Table 6 Sensitivity Analysis for Change from Baseline in 6MWD (m) – Study 044

Analysis/Treatment	n	Adjusted Mean Change from Baseline (SE)	Treatment Difference[a]	95% CI	p-value
MMRM OC (ITT)[b]					
Placebo	59	-52.65 (10.423)			
Drisapersen 6 mg/kg/wk	117	-42.32 (7.378)	10.334	(-14.645, 35.312)	0.415
MMRM OC (PP)[b]					
Placebo	53	-45.23 (10.413)			
Drisapersen 6 mg/kg/wk	99	-40.36 (7.589)	4.873	(-20.313, 30.059)	0.703
ANCOVA OC (ITT)[c]					
Placebo	59	-49.97 (10.732)			
Drisapersen 6 mg/kg/wk	117	-38.38 (7.739)	11.586	(-13.684, 36.855)	0.367
ANCOVA LOCF (ITT)[c]					
Placebo	60	-49.69 (10.593)			
Drisapersen 6 mg/kg/wk	125	-38.26 (7.531)	11.430	(-13.414, 36.274)	0.365
ANCOVA Multiple Imputed (MAR approach) (ITT)[d]					
Placebo	59	-50.27 (10.585)			
Drisapersen 6 mg/kg/wk	117	-40.24 (7.669)	10.026	(-15.036, 35.088)	0.430
ANCOVA Multiple Imputed (CIR approach) (ITT)[d]					
Placebo	59	-50.32 (10.588)			
Drisapersen 6 mg/kg/wk	117	-40.51 (7.656)	9.807	(-15.244, 34.858)	0.439

Data Source: Table 2.3, Table 2.4, Table 2.5, Table 2.6, Table 2.7.

ANCOVA=Analysis of Covariance, CIR=Copy Increment from Reference, LOCF=Last Observation Carried Forward, MAR=Missing at Random, MMRM=Mixed effect Model Repeated Measure, OC=Observed Cases.

a. Note a positive difference compared to placebo represents benefit over placebo.
b. Model includes terms for Treatment, Visit, Treatment by Visit, Country Grouping, Baseline 6MWD and Baseline 6MWD by Visit.
c. Model includes terms for Treatment, Country Grouping and Baseline 6MWD.
d. Model includes terms for Treatment, Visit, Treatment by Visit, Country Grouping and Baseline 6MWD.

Source: Clinical Study Report

Some patients lost ambulation during the trial and could not perform the 6MWD. A 0 value was recorded for the visits that a subject could not perform the 6MWD. Altogether, 14 subjects in the drisapersen group and 6 subjects in the placebo group had 0 values on 6MWD at one or more visits, resulted in a total of 29 visits with 0 values for subjects in the drisapersen group and 16 visits with 0 values for subjects in the placebo group. These 0 values resulted in large negative changes from baseline for these patients. Analysis removing these visits with 0 values was performed. The adjusted mean change from baseline was changed from -42.3 to -33.1 in the drisapersen group and was changed from -52.7 to -39.4 in the placebo group (compare Table 5 to Table 7). The impact of these patients in the drisapersen group did not appear to be larger than in the placebo group.

Table 7 Number (%) of patients / visits with 0 value in 6MWD assessment – Study 044

	Placebo N=61	Drisapersen 6 mg N=125
Number of patients with 0 in 6MWD	6 (9.8%)	14 (11.2%)
Number of visits with 0 in 6MWD	16 (6.6%)	29 (5.8%)
Analysis removing visits with 0 values		
Adjusted mean change at week 48	-39.4	-33.1
Treatment difference		6.33
Nominal p-value		0.5836

Source: Reviewer's analysis

Analysis of Secondary Endpoints

No secondary endpoints showed treatment benefit of drisapersen compared to placebo.

3.2.2 Evaluation of Study 117

3.2.2.1 Study Design – Study 117

The primary objective of the study was to assess the efficacy of 2 different dosing regimens of subcutaneous drisapersen administered over 24 weeks in ambulant subjects with DMD.

This was a phase 2, double-blind, placebo-controlled, parallel-group study in ambulant male subjects at least 5 years of age with DMD resulting from a mutation that was to be corrected by exon 51 skipping induced by drisapersen.

The active doses were:

- Continuous regimen; 6 mg/kg drisapersen once weekly
- Intermittent regimen; 6 mg/kg drisapersen twice weekly on 1st, 3rd and 5th weeks, once weekly on 2nd, 4th and 6th weeks, and no active drug on 7th to 10th week of each 10 week cycle

Similar to Study 044, there were 2 screening visits and a randomization/baseline visit at which 6MWD assessments were performed. The same criteria of 6MWD were applied.

Following a 2 to 4 week screening period, eligible patients were randomized into 2 parallel cohorts (the continuous regimen cohort and intermittent regimen cohort). Each cohort included subjects on drisapersen and matched placebo in a 2:1 ratio.

All subjects received a loading dosing regimen of twice weekly dosing with 6 mg/kg drisapersen for the first 3 weeks of treatment only. The intermittent regimen cycles started after completion of the loading dosing regimen (i.e. from Week 4). Subjects were treated for 48 weeks (including the loading dose period). At the end of the treatment period, subjects who completed the study had the option to enter an open-label extension study (Study DMD114349).

The study was fully blinded with respect to active drug and placebo in each cohort. The different regimens were not fully blinded. Subjects allocated to the continuous dosing regimen received a total of 51 doses of drisapersen or placebo, whereas subjects allocated to the intermittent regimen received a total of 50 doses of drisapersen or placebo.

The study aimed to randomize 54 subjects, which would provide 48 evaluable subjects assuming a drop-out rate of approximately 10%. This study was conducted at 13 centers in 9 non-US countries.

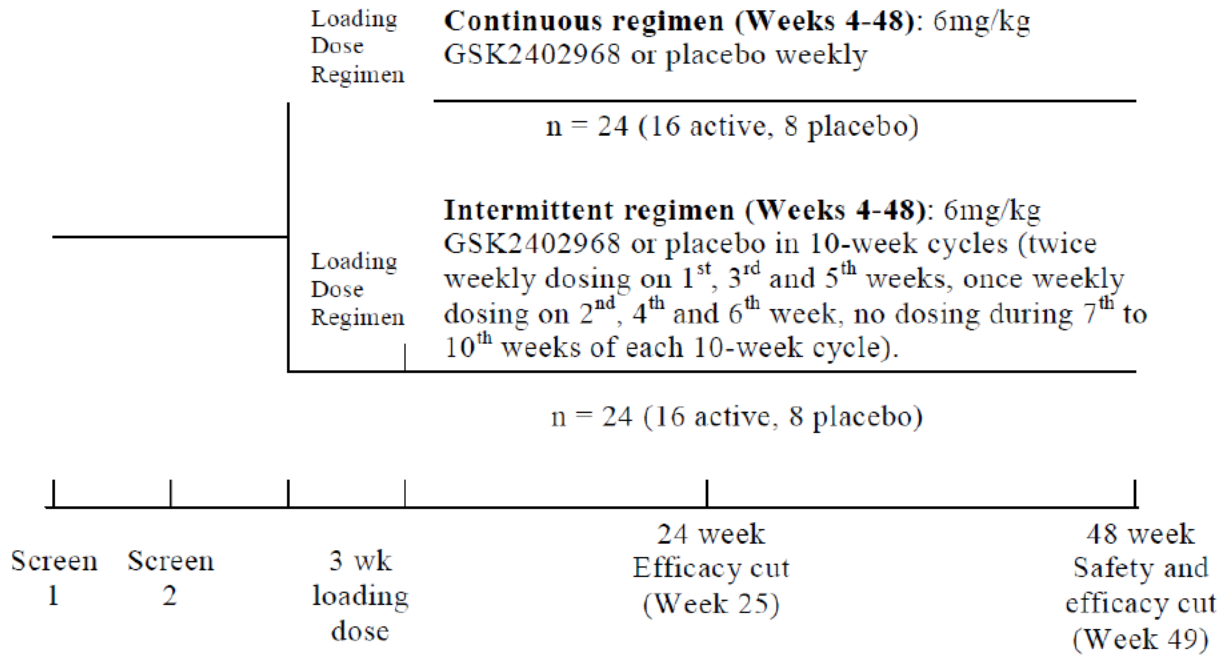

Figure 3 Study Schematic (Source: Clinical Study Report)

3.2.2.2 Study Endpoints – Study 117

The primary efficacy endpoint was muscle function using 6 minute walking distance (6MWD) test, the same endpoint used in Study 044.

The 6MWD was conducted at Screen 1, Screen 2, Baseline (Week 1), and Weeks 13, 25, 37 and 49. Refer to Section 3.2.1.2 for detailed description of 6MWD.

Secondary efficacy endpoints were:

- Timed function tests (times and grading): Grading of the 10 meter walk/run, the timed rising from floor and the 4-stair climb and descend was assessed on a 6 point scale
- Muscle strength (total score)
- North Star Ambulatory Assessment (NSAA)

- Frequency of accidental falls (during 6MWD)
- Time to loss of ambulation
- Creatine kinase serum concentrations
- Pulmonary function (FEV1, FVC, MIP, MEP, PCF and PF)
- Dystrophin expression (muscle biopsies)

3.2.2.3 Statistical Methodologies – Study 117

The primary efficacy endpoint was the change from baseline at Week 25 in the 6MWD.

The primary population for efficacy evaluation was the ITT population (see Section 3.2.1.3). The observed case (OC) data from the ITT population was analyzed using a mixed model for repeated measures (MMRM) with restricted maximum likelihood estimation and an unstructured covariance matrix. The model included treatment, visit, treatment-by-visit interaction, center/country grouping, baseline 6MWD and baseline 6MWD-by-visit interaction as fixed effects. Separate comparisons were made for each treatment regimen versus placebo. Due to the two different treatment regimens, the type 1 error rate was preserved by utilizing the Bonferroni-Holm adjustment. The p-values from the two primary analyses (6 mg/kg drisapersen continuous vs. placebo, and 6 mg/kg drisapersen intermittent vs. placebo), were ordered smallest to largest. The smallest p-value was compared to a significance level of $\alpha/2$ (0.025). If the result was demonstrated to be statistically significant at this level, i.e. $p<0.025$, then the second p-value was compared to a significance level of α (0.05). If the initial comparison showed the result not to reach statistical significance, then the second comparison was also considered not to have reached statistical significance.

The following sensitivity analyses were to be performed to examine the robustness of the results in the presence of missing data, and to determine the impact of protocol violators.

1. Analysis of covariance (ANCOVA) utilizing the OC data, for the ITT population.
2. ANCOVA utilizing last observation carried forward (LOCF) data, for the ITT population.
3. ANCOVA utilizing data imputed via multiple imputation, for the ITT population.
4. MMRM analysis utilizing the OC data for the PP population.

The ANCOVA models included fixed terms for treatment group, baseline 6MWD, and country/center grouping.

The data from all secondary endpoints were summarized. In addition, the analyses detailed below were to be performed.

Continuous Endpoints

Each secondary endpoint was analyzed for the OC dataset using a mixed model for repeated measures (MMRM). The MMRM model for each secondary endpoint included fixed terms for treatment, visit, treatment-by-visit interaction, country/country group, baseline score, and baseline score by visit.

Time to Event Endpoints

The time to loss of ambulation was to be analyzed if ≥ 4 subjects in any treatment group (placebo group combined) experienced a loss of ambulation. Kaplan-Meier estimates, their associated plot, and a Log-Rank test were to be produced.

3.2.2.4 Study Population Results – Study 117

3.2.2.4.1 Patient Disposition

A total of 53 subjects were randomized at 13 centers in 9 countries to one of the three treatment arms: 18 in drisapersen 6 mg/kg continuous group, 17 in drisapersen 6 mg/kg intermittent group, and 18 in combined placebo group. All subjects completed the study.

3.2.2.4.2 Patient Demographic and Baseline Characteristics

Subject demographics are presented in Table 8. Subjects in drisapersen 6 mg/kg intermittent group were slightly older on average than the subjects in the other two treatment groups. All patients were male, and the majority of patients were Caucasians.

Table 8 Summary of Demographic Characteristics (Safety Population) – Study 117

	Placebo (combined) N=18	Drisapersen continuous N=18	Drisapersen intermittent N=17
Age (years)			
Mean (SD)	6.9 (1.18)	7.2 (1.66)	7.7 (1.49)
Median	7.0	6.5	8.0
Min, Max	5, 9	5, 11	5, 10
Sex, n (%)			
Male	18 (100)	18 (100)	17 (100)
Race, n (%)			
White – Caucasian	13 (72)	15 (83)	14 (82)
Other	3 (17)	2 (11)	1 (6)
Not collected	2 (11)	1 (6)	2 (12)

Source: Clinical Study Report

Baseline DMD characteristics of patients are summarized in Table 9. Patients in the 6 mg/kg continuous group had their first symptom slightly more recently and had higher baseline 6MWD than the other two treatment groups.

Table 9 Summary of Baseline DMD Characteristics (Safety Population) – Study 117

	Placebo (combined) (N=18)	6 mg/kg Drisapersen Continuous (N=18)	6 mg/kg Drisapersen Intermittent (N=17)	Total (N=53)
Time Since First Symptoms (months)[a]				
Mean (SD)	63.5 (24.00)	61.1 (24.86)	64.5 (24.56)	63.0 (24.04)
Median	73.3	57.4	63.1	62.2
Min, Max	15, 95	27, 112	27, 105	15, 112
Time Since Diagnosis (months)[a]				
Mean (SD)	44.4 (21.61)	44.6 (27.69)	47.8 (26.48)	45.5 (24.93)
Median	35.5	41.4	47.0	43.4
Min, Max	12, 82	3, 96	3, 105	3, 105
Time Since First Corticosteroid Taken (months)[a]				
Mean (SD)	24.2 (14.02)	26.0 (21.20)	32.6 (17.04)	27.5 (17.72)
Median	22.5	13.7	33.8	25.6
Min, Max	7, 60	7, 69	7, 63	7, 69
Corticosteroid Regimen[b]				
Continuous	11 (61)	12 (67)	9 (53)	32 (60)
Intermittent	7 (39)	6 (33)	8 (47)	21 (40)
6MWD (m)				
Mean	403.18	427.61	394.57	NA
(SD)	(45.131)	(70.045)	(66.952)	

Source: Clinical Study Report

3.2.2.5 Efficacy Results – Study 117

Primary Analysis

In the primary efficacy MMRM analysis of change from baseline in 6MWD (m) at Week 25, a statistically significant treatment benefit (35.09 m; $p<0.025$) over combined placebo in 6MWD was observed for the continuous regimen (Table 10 and Figure 4). No statistically significant or clinically meaningful treatment benefit over placebo at Week 25 was observed for the intermittent regimen.

Table 10 Summary of MMRM Analysis of Change from Baseline in 6MWD – Study 117

	Placebo (combined) (N=18)	6 mg/kg Drisapersen Continuous (N=18)	6 mg/kg Drisapersen Intermittent (N=17)
Baseline			
n	18	18	17
Mean (SD)	403.18 (45.131)	427.61 (70.045)	394.57 (66.952)
Week 25			
n	16	16	15
Adjusted mean change (SE)	-3.6 (9.73)	31.5 (9.75)	-0.1 (10.34)
Adjusted mean difference vs. placebo		35.09	3.51
95% CI		(7.59, 62.60)	(-24.34, 31.35)
p-value		0.014	0.801

Source: Clinical Study Report

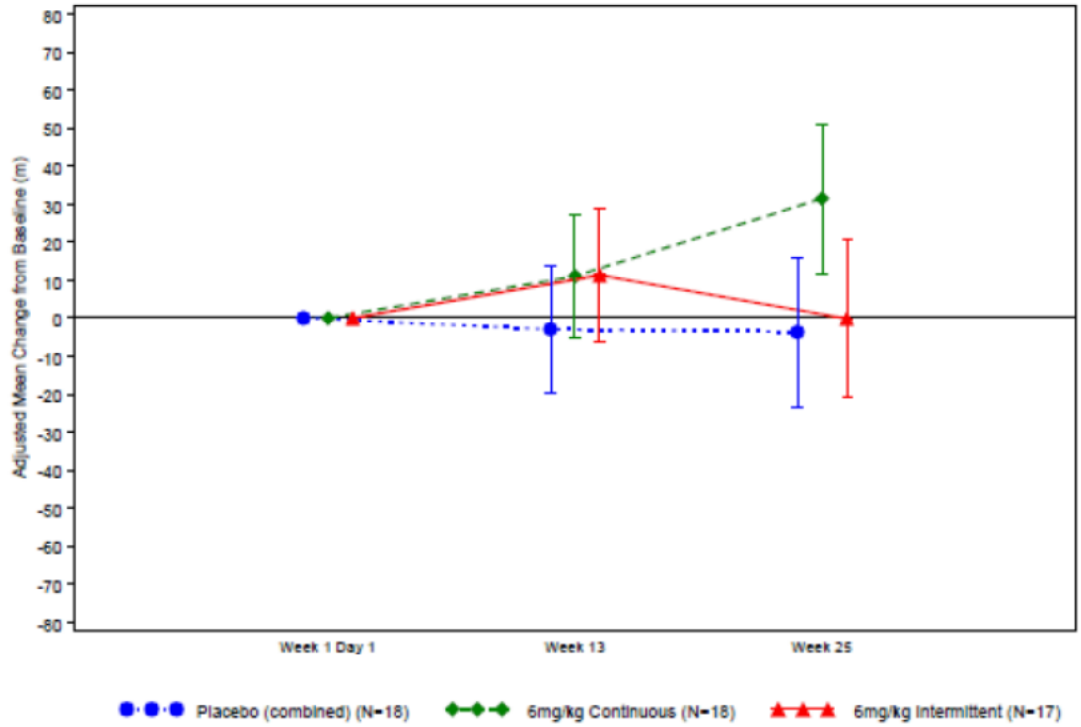

Figure 4 MMRM Analysis of Change from Baseline in 6MWD (m) at Week 25 (ITT Population)
Source: Clinical Study Report

In the sponsor's analysis reported above, 6 patients had their week 25 assessments excluded. All 6 patients completed the study and assessments. The exclusion of their data was resulted from a tight assessment window of 6 days. Five of the 6 patients (2 in each group) had their week 25 assessment performed at week 24, and one was performed at week 27. Analysis including week

25 assessments of these 6 patients resulted in a treatment difference of 31.2 m (p=0.022) between the continuous regiment and placebo and a treatment difference of 13.3 m (p=0.534) between the intermittent regiment and placebo.

The treatment difference between the continuous regiment and intermittent regiment was 22.9 m with a nominal p-value of 0.098. It was not clear what caused the discrepancy in treatment effect between the continuous regiment and intermittent regiment, as the total exposures for the two regimens were about the same. It is worth noting that leading into the week 25 assessment, there was an empty dosing period of 4 weeks from week 20 to week 23 for the drisapersen intermittent group due to the 10-week dosing cycle.

Sensitivity Analyses of the Primary Endpoint

Further comparisons of the drisapersen continuous dosing regimen with placebo for the primary efficacy endpoint at Week 25 were made by the sponsor to assess the sensitivity of the primary analysis. Results are presented in Table 11. Except for the analysis noted in footnote d (unslotted), analyses presented in Table 11 excluded 6 patients who had Week 25 visit outside the visit window.

Table 11 6 mg/kg Drisapersen Continuous Regimen Sensitivity Analyses: Change from Baseline in 6MWD (m) at Week 25 – Study 117

Analysis	Population	Dataset	Treatment Difference	95% CI	P-value
MMRM[a]	ITT	OC	35.09	(7.59, 62.60)	0.014
MMRM[a]	PP	OC	37.83	(8.31, 67.34)	0.013
ANCOVA[b]	ITT	OC	35.25	(7.41, 63.08)	0.014
ANCOVA[b]	ITT	LOCF	30.63	(3.77, 57.49)	0.026
MMRM[a]	ITT	OC (unslotted)[d]	31.19	(4.70, 57.67)	0.022
MMRM[a]	ITT	OC (exc. outlier)[c]	30.69	(3.85, 57.53)	0.026
MMRM[a], Uncombined Placebo	ITT	OC	46.78	(11.93, 81.63)	0.010

Source: Week 25 Analysis Table 2.3, Week 25 Analysis Table 2.10, Week 25 Analysis Table 2.7, Week 25 Analysis Table 2.8, Week 25 Analysis Table 2.60, Week 25 Analysis Table 2.62, and Week 25 Analysis Table 2.65.

a. Model includes terms for Treatment, Visit, Treatment by Visit, Country Grouping, Baseline 6MWD and Baseline 6MWD by Visit.
b. Model includes terms for Treatment, Country Grouping and Baseline 6MWD.
c. Subject 3002, randomised to placebo intermittent, was determined to be an outlier (6MWD of 322 m, 432.2 m and 265 m at Baseline, Week 13 and Week 25 respectively).
d. For reporting purposes, efficacy data were slotted to pre-defined visit windows, based on the time of the assessment since first dose. Where a visit was attending particularly early or late, the assessment would have fallen outside of the visit window and was thus excluded from analyses. This analysis of unslotted data, analysed the data according to the investigator recorded visit, regardless of the time at which this occurred.

Source: Clinical Study Report

Numerical differences in 6MWD between placebo continuous regimen and placebo intermittent regimen were observed. The following table presents the results where the two regimens of placebo were analyzed separately.

Table 12 Summary of MMRM Analysis of Change from Baseline in 6MWD (m) – Placebo Group Analyzed separately – Study 117

	Placebo Continuous (N=9)	Placebo Intermittent (N=9)	6 mg/kg Drisapersen Continuous (N=18)	6 mg/kg Drisapersen Intermittent (N=17)
Baseline				
n	9	9	18	17
Mean (SD)	405.90 (49.365)	400.46 (43.297)	427.61 (70.045)	394.57 (66.952)
Week 25				
n	7	9	16	15
Adjusted mean change (SE)	-15.2 (14.37)	6.1 12.99	31.6 (9.72)	0.3 (10.32)
Adjusted mean difference vs. placebo			46.78	-5.81
95% CI			(11.93, 81.63)	(-38.26, 26.64)
p-value			0.010	0.720
Week 49				
n	9	8	18	15
Adjusted mean change (SE)	-35.9 (17.67)	-13.2 (18.16)	11.2 (12.65)	2.8 (13.65)
Adjusted mean difference vs. placebo			47.14	15.95
95% CI			(3.54, 90.75)	(-29.03, 60.92)
p-value			0.035	0.479

Source: Clinical Study Report

Due to the small sample size, it was difficult to determine whether or not the difference was due to reasons other than variation.

Variations among the 3 Pre-treatment Assessment Values

Large within-subject variations in 6MWD assessments were observed in the three pre-treatment visits (Screen 1, Screen 2 and Baseline). The study required that the 3 pre-treatment 6MWD had to be within 20% of each other, which could result in a difference of as much as 100 meters.

In order to examine whether the choice of baseline had an impact on the efficacy results, the average score of the 3 pre-treatment 6MWD assessments was obtained for each patient and used as the baseline in the primary analysis model. The analysis included all patients (including 6 patients with assessments outside the visit window).

As shown in the following table, the average scores of the pre-treatment 6MWDs were close to the baseline values for the placebo and drisapersen continuous groups, and average score was a little higher than the baseline for the intermittent group. The adjusted mean difference for 6

mg/kg continuous groups vs. placebo was a little smaller when average pre-treatment score was used as baseline, but findings generally agreed with the results from the primary analysis.

Table 13 Analysis of 6MWD using average of the pre-treatment assessments as baseline – Study 117

6MWD	Placebo (combined) N=18	6 mg/kg Drisapersen Continuous N=18	6 mg/kg Drisapersen Intermittent N=17
Baseline			
Mean	403.2	427.6	394.6
Median	400.0	425.0	381.0
Average of Pre-treatment			
Mean	400.4	427.6	402.4
Median	402.7	429.3	395.0
Week 25			
Adjusted mean change	-2.2	22.7	-4.4
Adjusted mean diff vs. placebo		24.9	-2.1
p-value		0.051	0.864

Source: Reviewer's analysis

Week 49 Analysis of 6MWD

An MMRM analysis was also conducted for the 6MWD including all data at Week 49. The model was analogous to that performed for the primary analysis at Week 25. Numerical treatment differences of 35.84 m and 27.08 m were observed for the continuous and intermittent groups respectively at Week 49 (Table 14 and Figure 5).

Table 14 Summary of MMRM Analysis of Change from Baseline in 6MWD (m) at Week 49 – Study 117

	Placebo (combined) (N=18)	6 mg/kg Drisapersen Continuous (N=18)	6 mg/kg Drisapersen Intermittent (N=17)
Baseline			
n	18	18	17
Mean (SD)	403.18 (45.131)	427.61 (70.045)	394.57 (66.952)
Week 25			
n	16	16	15
Adjusted mean change (SE)	-3.6 (9.73)	31.5 (9.75)	-0.1 (10.34)
Adjusted mean difference vs. placebo		35.09	3.51
95% CI		(7.59, 62.60)	(-24.34, 31.35)
p-value		0.014	0.801
Week 49			
n	17	18	15
Adjusted mean change (SE)	-24.7 (12.75)	11.2 (12.64)	2.4 (13.63)
Adjusted mean difference vs. placebo		35.84	27.08
95% CI		(-0.11, 71.78)	(-9.83, 63.99)
p-value		0.051	0.147

Source: Clinical Study Report

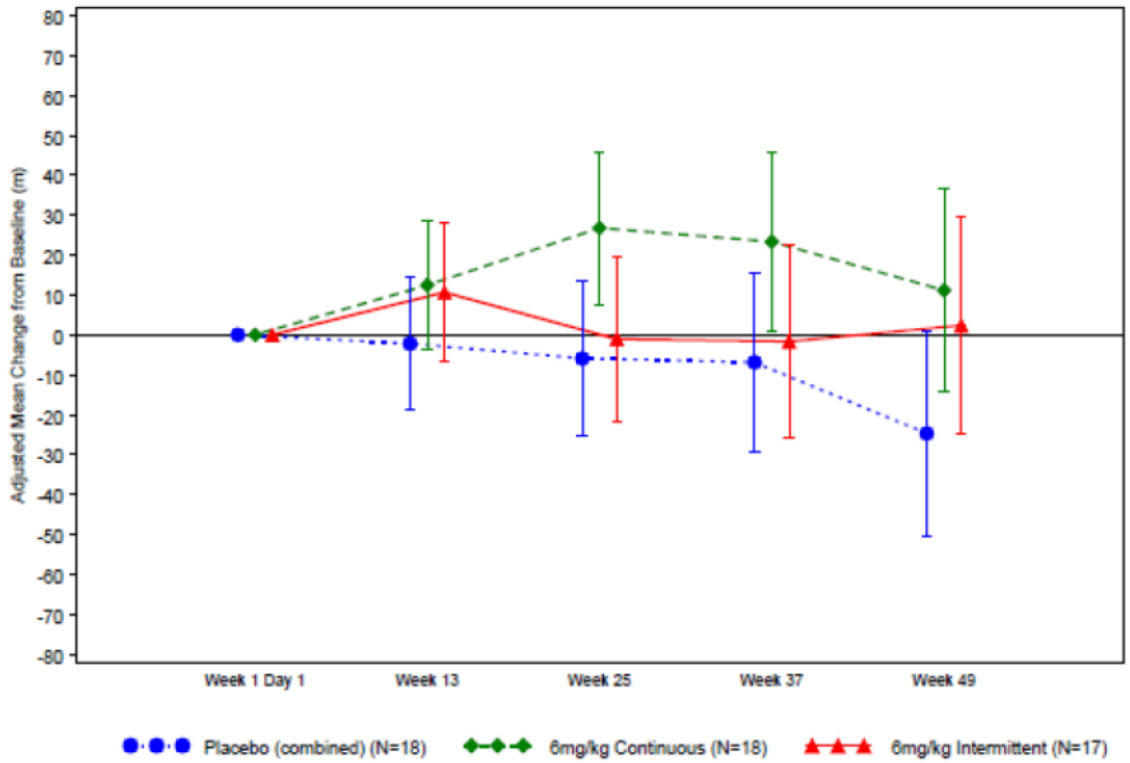

Figure 5 MMRM Analysis of Change from Baseline in 6MWD (m) at Week 49
Source: Clinical Study Report

Efficacy of Secondary Endpoints

None of the secondary endpoints reached nominal significance in treatment difference.

3.2.3 Evaluation of Study 876

3.2.3.1 Study Design – Study 876

This was a phase 2, double blind, parallel-group, placebo-controlled study in ambulant subjects with DMD resulting from a mutation that was to be corrected by exon 51 skipping induced by drisapersen.

Similar to Studies 044 and 117, there were 2 screening visits and a randomization visit at which 6MWD was performed. Subjects received drisapersen 3 mg/kg, drisapersen 6 mg/kg, drisapersen 3 mg/kg volume-matched placebo, or drisapersen 6 mg/kg volume-matched placebo (2:2:1:1 ratio) given SC once a week for 24 weeks. After the last dose of drisapersen /placebo, subjects continued into a 24 week post-treatment period. At the end of the post-treatment period, subjects who completed the study had the option to enter an open-label extension study.

A schematic of the study design is presented in Figure 6.

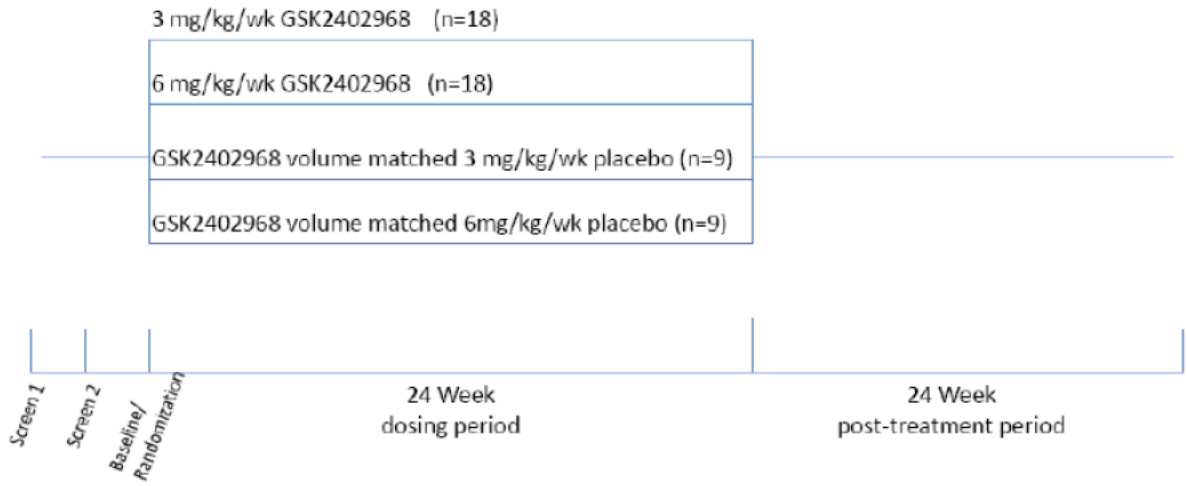

Figure 6 Study Schematic
Source: Clinical Study Report

The study was fully blinded with respect to active and placebo; however the study was not fully blinded to dose. Subjects allocated to the 3mg/kg or volume-matched placebo arms received a lower volume of injection than those allocated to the 6 mg/kg or volume-matched placebo arms.

This study was conducted in pediatric males aged 5 and up at 13 centers in the United States.

3.2.3.2 Study Endpoints – Study 876

The primary efficacy endpoint was muscle function using the 6 minute walking distance (6MWD) test. Refer to Section 3.2.1.2 for detailed description of 6MWD assessment.

A group of similar secondary endpoints as in Study 117 were included.

- Clinician Global Impression of Improvement (CGI-I) (Study 876)
- Functional Outcomes Assessments (Study 876)

3.2.3.3 Statistical Methodologies – Study 876

Change from baseline in the 6MWD was analyzed for the observed cases (OC) of ITT patient population dataset using a mixed model for repeated measures (MMRM). The MMRM model for change from baseline in 6MWD included fixed categorical terms for treatment, visit, treatment-by-visit interaction, center grouping, and continuous fixed covariates of baseline 6MWD and baseline 6MWD-by-visit interaction.

Primary inferences regarding treatment differences for the changes from baseline in the 6MWD was derived from the MMRM models at Week 24. As additional supportive information, treatment differences for Week 12 were also estimated using the MMRM models. Separate comparisons were made for each dose versus placebo. Due to the two different doses, the type 1 error rate was preserved by utilizing a hierarchical approach. The difference between the 6 mg/kg dose of drisapersen was assessed first. If a statistically significant difference was observed conclusions could be drawn regarding the significance of the 3mg/kg dose versus placebo. If no statistically significant difference was observed between the 6 mg/kg dose and placebo, then further analyses of the 3mg/kg dose were considered exploratory, and no conclusions regarding the statistical significance of the treatment difference were made.

Same sensitivity analyses as used in Study 117 were performed.

3.2.3.4 Study Population Results – Study 876

3.2.3.4.1 Patient Disposition

A total of 51 subjects were randomized at 13 centers in the United States. All subjects completed the study.

One subject in the placebo group (000158) had the treatment blind broken during Week 7.

3.2.3.4.2 Patient Demographic and Baseline Characteristics

Patient's demographic characteristics are presented in Table 15. Patients in drisapersen 6 mg/kg group had lower median age of 6.5 years but included a 13 year old patient. In comparison, the median age was 8 years with maximum age of 11 years in the other two treatment groups.

Table 15 Summary of Demographic Characteristics – Study 876

	Placebo (combined) N=16	**Drisapersen 3 mg N=17**	**Drisapersen 6 mg N=18**
Age (years)			
Mean (SD)	8.0 (1.79)	7.8 (1.91)	7.6 (2.70)
Median	8.0	8.0	6.5
Min, Max	5, 11	5, 11	5, 13
Sex, n (%)			
Male	16 (100)	17 (100)	18 (100)
Race, n (%)			
White/Caucasian/European	14 (88)	16 (94)	15 (83)
Other	2 (12)	1 (6)	3 (17)

Source: Clinical Study Report

Table 16 presents the baseline DMD characteristics of patients. The mean baseline 6MWD value was about 20 meters lower in the drisapersen 6 mg/kg group compared to the other two treatment groups.

Table 16 Summary of Muscular Dystrophy Disease Characteristics – Study 876

	Number (%) of Subjects			
	Placebo (combined) (N=16)	Drisapersen 3 mg/kg (N=17)	Drisapersen 6 mg/kg (N=18)	Total (N=51)
Time Since First Symptoms (months)[a]				
Mean (SD)	57.3 (29.68)	67.3 (27.13)	59.0 (29.50)	61.2 (28.55)
Median	59.6	60.4	60.0	60.4
Min., Max	13, 112	25, 124	8, 112	8, 124
Time Since Diagnosis (months)[a]				
Mean (SD)	45.5 (29.70)	47.1 (26.35)	46.5 (26.76)	46.4 (27.03)
Median	44.5	38.3	46.2	43.3
Min., Max.	9, 111	13, 108	7, 96	7, 111
Time Since First Corticosteroid Taken (months)[a]				
Mean (SD)	37.1 (24.31)	33.3 (15.98)	26.8 (22.51)	32.2 (21.21)
Median	38.9	28.0	18.5	26.9
Min., Max.	7, 85	8, 58	6, 81	6, 85
Corticosteroid Regimen[b]				
Continuous	15 (94)	15 (88)	18 (100)	48 (94)
Intermittent	1 (6)	2 (12)	0	3 (6)
6MWD (m)				
Mean	416.41	415.21	396.18	NA
(SD)	(56.988)	(58.049)	(60.662)	NA

Source: Clinical Study Report

3.2.3.5 Efficacy Results – Study 876

Analysis of the Primary Endpoint

In the primary efficacy MMRM analysis of change from baseline in 6MWD at Week 24, a numerical treatment difference of 27.10 meters over placebo was observed for the 6 mg/kg drisapersen group (Table 17 and Figure 7). This result was not statistically significant (p=0.069). The adjusted mean change at Week 24 for the drisapersen 3 mg/kg group was numerically lower than the placebo group. Results from sensitivity analyses were similar to the one from the primary analysis.

Table 17 Summary of Repeated Measures Analysis of Change from Baseline in 6MWD – Study 876

	Placebo (combined) (N=16)	Drisapersen 3 mg/kg (N=17)	Drisapersen 6 mg/kg (N=18)
Baseline			
n	16	17	18
Mean (SD)	416.41 (56.988)	415.21 (58.049)	396.18 (60.662)
Week 12			
n	16	17	18
Adjusted mean change (SE)	-4.70 (10.643)	-6.60 (9.941)	14.98 (9.919)
Adjusted mean difference vs. placebo	NA	-1.896	19.679
95% CI	NA	(-32.009, 28.217)	(-9.566, 48.924
p-value	NA	0.900	0.182
Week 24			
n	16	17	18
Adjusted mean change (SE)	-10.98 (10.666)	-19.93 (9.964)	16.12 (9.941)
Adjusted mean difference vs. placebo	NA	-8.946	27.099
95% CI	NA	(-39.122, 21.229)	(-2.210, 56.408)
p-value	NA	0.554	0.069

Source: Clinical Study Report

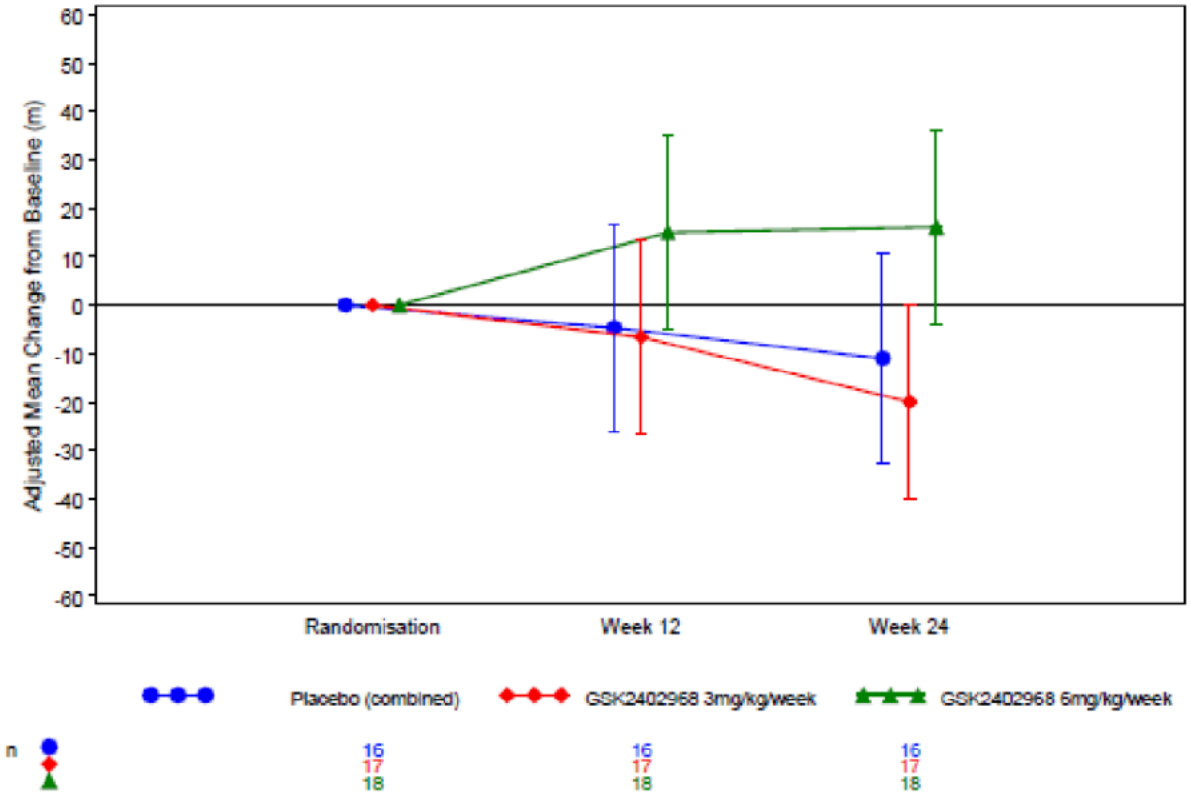

Figure 7 MMRM Analysis of Change from Baseline in 6MWD at Week 24
Source: Clinical Study Report

Sensitivity analyses similar to the ones performed in Study 117 were conducted and results were generally consistent with the one from primary analysis (Table 18).

Table 18 Sensitivity Analyses: Change from Baseline in 6MWD (m) at Week 24 – Study 876

Analysis	Population	Dataset	Treatment Difference	95% CI	P-value
Drisapersen 3 mg/kg/wk					
MMRM[a]	ITT	OC	-8.945	(-39.12, 21.23)	0.554
MMRM[a]	PP	OC	-16.43	(-49.36, 16.49)	0.319
ANCOVA[b]	ITT	OC	-9.26	(-39.92, 21.39)	0.546
ANCOVA[b]	ITT	LOCF	-9.26	(-2.72, 56.63)	0.546
Drisapersen 6 mg/kg/wk					
MMRM[a]	ITT	OC	27.10	(-2.21, 56.41)	0.069
MMRM[a]	PP	OC	19.43	(-11.58, 50.44)	0.213
ANCOVA[b]	ITT	OC	26.95	(-2.72, 56.63)	0.074
ANCOVA[b]	ITT	LOCF	26.95	(-2.72, 56.63)	0.074

Data Source: Week 24 Analysis Table 2.3, Week 24 Analysis Table 2.4, Week 24 Analysis Table 2.5, Week 24 Analysis Table 2.6

a. Model included terms for Treatment, Visit, Treatment by Visit, Baseline 6MWD and Baseline 6MWD by Visit.
b. Model included terms for Treatment and Baseline 6MWD.

Source: Clinical Study Report

Similar to Study 117, within-subject variations in 6MWD assessments were observed in the three pre-treatment visits and analysis using average score of the 3 pre-treatment 6MWD assessments as baseline was performed.

Difference between the average pre-treatment 6MWD score and baseline 6MWD was small in average, and adjusted treatment differences between each of the drisapersen dose group compared to placebo were similar to what were obtained from the primary analysis (Table 19).

Table 19 Analysis of 6MWD using average of the pre-treatment assessments as baseline – Study 876

6MWD	Placebo (combined) N=16	Drisapersen 3 mg/kg N=17	Drisapersen 6 mg/kg N=18
Baseline			
Mean	416.4	415.2	396.2
Median	420.0	403.0	396.0
Average of Pre-treatment			
Mean	419.2	414.3	400.0
Median	428.8	396.7	396.7
Week 25			
Adjusted mean change	-15.3	-19.3	13.6
Adjusted mean diff vs. placebo		-4.1	28.9
p-value		0.775	0.042

Source: Reviewer's analysis

No discrepancies were found in the two placebo matched dose groups.

An MMRM analysis was also conducted for the 6MWD including all data up to Week 48. The model was analogous to that performed for the primary analysis at Week 24. Numerical treatment differences of -24.75 m and 27.87 m were observed for the drisapersen 3 mg/kg and drisapersen 6 mg/kg groups respectively at Week 48 (Table 20).

Table 20 Summary of Repeated Measures Analysis of Change from Baseline in 6MWD – Study 876

	Placebo (combined) (N=16)	Drisapersen 3 mg/kg (N=17)	Drisapersen 6 mg/kg (N=18)
Baseline			
n	16	17	18
Mean (SD)	416.41 (56.988)	415.21 (58.049)	396.18 (60.662)
Week 12			
n	16	17	18
Adjusted mean change (SE)	-3.54 (10.617)	-7.45 (9.923)	15.92 (9.898)
Adjusted mean difference vs. placebo	NA	-3.914	19.458
95% CI	NA	(-33.933, 26.104)	(-9.709, 48.626)
p-value	NA	0.794	0.186
Week 24			
n	16	17	18
Adjusted mean change (SE)	-9.82 (10.660)	-20.79 (9.966)	17.06 (9.940)
Adjusted mean difference vs. placebo	NA	-10.965	26.879
95% CI	NA	(-41.107, 19.177)	(-2.416, 56.174)
p-value	NA	0.468	0.071
Week 36			
n	15	16	18
Adjusted mean change (SE)	-8.72 (13.114)	-26.58 (12.395)	19.41 (12.226)
Adjusted mean difference vs. Placebo	NA	-17.864	28.133
95% CI	NA	(-54.868, 19.139)	(-8.156, 64.422)
p-value	NA	0.335	0.125
Week 48 (end of post treatment period)			
n	15	17	18
Adjusted mean change (SE)	-13.17 (14.843)	-37.92 (14.059)	14.69 (13.891)
Adjusted mean difference vs. placebo	NA	-24.750	27.866
95% CI	NA	(-66.371, 16.871)	(-13.043, 68.775)
p-value	NA	0.238	0.177

Source: Clinical Study Report

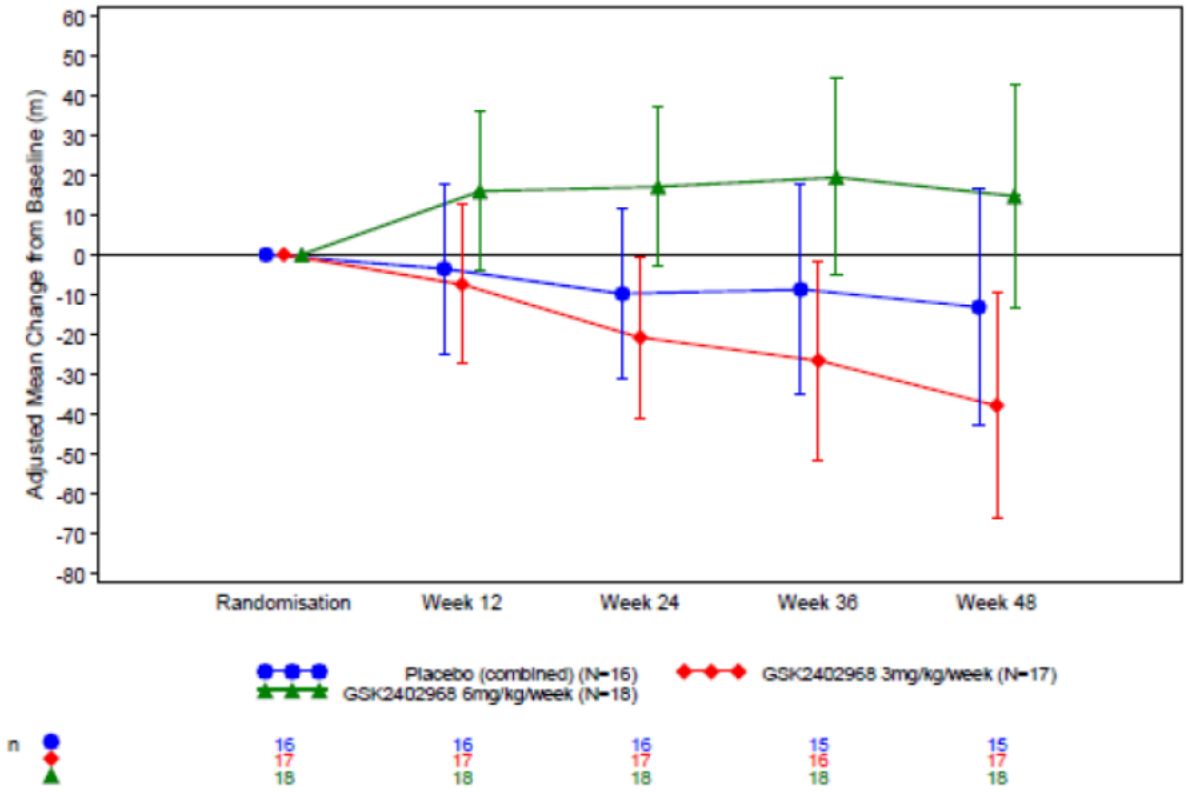

Figure 8 MMRM Analysis of Change from Baseline in 6MWD (m) at Week 48
Source: Clinical Study Report

Analysis of Secondary Endpoints

None of the secondary endpoints reached nominal significance in treatment benefit.

3.3 Evaluation of Safety

Refer to Safety Review by Dr. Evelyn Mentari and Clinical Review by Dr. Veneeta Tandon for Evaluation of Safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

All subjects were male and no analysis was performed with respect to gender difference. Analysis by race was not performed either as the majority of patients were Caucasians.

It was believed that subjects at age 7 or under do markedly better than subjects older than 7 years of age generally. Therefore, subjects were grouped by ≤ 7, 7 to 10, and > 10 years in age in Study 044. Few subjects were older than 10 years of age and subjects were grouped by ≤ 7 and > 7 years in age in Studies 117 and 876.

Analysis of Efficacy by Subgroups - Study 044

In general, younger patients did markedly better than older patients as was believed. It appeared that 6 mg/kg drisapersen group had more patients in the older age group and fewer patients in the younger age group. An analysis including age group in the model was performed. The results were similar (treatment difference =11.7 meters; p=0.349) to the ones from the primary analysis in the change from baseline in 6MWD. See more discussions on age effect in the next section.

Numerically, the 6 mg/kg drisapersen group had smaller decreases (or better results) in 6MWD than the placebo group on average in the Eastern and Northern European sites, but the group did poorly (worse than placebo) in sites in Asia, Canada and Southern Europe.

Table 21 Change from Baseline in 6MWD (m) by Demographic Characteristics – Study 044

	Placebo N=60	Drisapersen 6 mg N=125
Age ≤ 7		
N (%)	29 (48.3)	51 (40.8)
Baseline mean (median)	382.8 (373.0)	367.9 (372.9)
Week 48 mean (median)	358.9 (365.1)	367.6 (384.0)
Adjusted mean change	-25.3	-3.8
7 < Age ≤ 10		
N (%)	25 (41.7)	53 (42.4)
Baseline mean (median)	320.9 (325.9)	333.4 (361.0)
Week 48 mean (median)	239.1 (224.0)	270.6 (323.8)
Adjusted mean change	-79.9	-71.7
Age > 10		
N (%)	6 (10.0%)	21 (16.8)
Baseline mean (median)	295.3 (261.1)	273.8 (261.9)
Week 48 mean (median)	219.6 (172.3)	195.6 (200.0)
Adjusted mean change	-81.7	-94.3
Asia		
N (%)	7 (11.7)	16 (12.8)
Baseline mean (median)	301.8 (285.0)	325.4 (328.0)
Week 48 mean (median)	254.6 (277.0)	279.4 (338.5)
Adjusted mean change	-39.9	-49.2
Canada		
N (%)	6 (10.0)	13 (10.4)
Baseline mean (median)	377.3 (376.5)	386.3 (383.0)
Week 48 mean (median)	380.4 (407.0)	362.2 (385.0)
Adjusted mean change	13.7	-27.1

Northern Europe		
N (%)	11 (18.3)	22 (17.6)
Baseline mean (median)	367.4 (369.0)	352.1 (358.5)
Week 48 mean (median)	285.2 (317.0)	325.7 (346.3)
Adjusted mean change	-87.0	-24.3*
Russia & Eastern Europe		
N (%)	7 (11.7)	12 (9.6)
Baseline mean (median)	353.8 (355.0)	380.5 (383.3)
Week 48 mean (median)	284.0 (311.0)	379.0 (371.4)
Adjusted mean change	-70.1	-1.3
South America		
N (%)	8 (13.3)	21 (16.8)
Baseline mean (median)	280.8 (292.1)	260.7 (278.0)
Week 48 mean (median)	220.2 (198.2)	206.7 (244.4) (n=18)
Adjusted mean change	-63.3	-59.3
Southern Europe		
N (%)	20 (33.3)	37 (29.6)
Baseline mean (median)	377.2 (374.0)	360.0 (400.0)
Week 48 mean (median)	326.7 (368.6)	295.1 (343.8)
Adjusted mean change	-54.5	-63.7

Source: Reviewer's analysis

Analysis of Efficacy by Subgroups - Study 117

Patients in Study 117 were generally younger than the patients in Study 044. All but one patient was older than 10 years of age.

It should be noted that this study had only 53 patients in total. Once divided into subgroups, variation could play a big role. Therefore, one should be cautious in interpreting the results presented in this section.

The results presented in this and the next section are different from what were obtained by the sponsor as 6 patients were excluded in the sponsor's analysis due to visit outside the window, which I believe was not appropriate.

In this study, drisapersen intermittent regimen had larger proportion of patients in the older age group compared to the other two groups. However, this group, although with lower baseline 6MWD scores, was responding to the treatment slightly better than the younger age group numerically.

The adjusted mean change from baseline for the younger age group and older age group appeared to be similar in the two drisapersen groups. However, in the placebo group, the older age subjects appeared to be doing more poorly than the younger age ones.

Compared to Study 044, the patient population in Study 117 appeared to be younger and less impaired, and age did not appear to have negatively impacted treatment effect as large treatment differences between active drug groups versus placebo were observed in the older age patients.

Table 22 Change from Baseline in 6MWD (m) by Demographic Characteristics – Study 117

	Placebo (combined) N=18	6 mg/kg Drisapersen Continuous N=18	6 mg/kg Drisapersen Intermittent N=17
Age ≤ 7			
N (%)	13 (72.2)	11 (61.1)	7 (41.2)
Mean Baseline	409.6	413.4	414.1
Adjusted Mean Change	7.0	26.7	-3.9
Adjusted diff vs. placebo		19.8	-10.9
Age > 7			
N	5 (27.8)	7 (38.9)	10 (58.8)
Mean Baseline	386.4	449.9	380.9
Adjusted Mean Change	-43.7	25.5	6.4
Adjusted diff vs. placebo		69.1	50.1
Australia, UK, Belgium, Netherlands			
N	10 (55.6)	8 (44.4)	8 (47.1)
Mean Baseline	378.7	403.9	401.0
Adjusted Mean Change	-15.4	20.3	3.8
Adjusted diff vs. placebo		35.7	19.2
Spain, France, Germany			
N		6	7
Mean Baseline	5	466.8	394.5
Adjusted Mean Change	445.8	18.3	-21.1
Adjusted diff vs. placebo	-11.1	29.4	-10.0
Turkey and Israel			
N		4	2
Mean Baseline	3	416.3	369.2
Adjusted Mean Change	413.7	36.6	14.6
Adjusted diff vs. placebo	32.5	4.0	-17.9

Source: Reviewer's analysis

Analysis of Efficacy by Subgroups - Study 876

Study 876 was conducted in US, and no analysis by region was performed.

In Study 876, there were 6 patients who were older than 10 at the baseline. The mean baseline 6MWD score for the older age group was slightly higher in 6 mg/kg drisapersen group, but was about 45 meters lower in each of the other two groups, compared to the mean baseline 6MWD in the younger age group. No large differences in the adjusted mean change in 6MWD were found between the younger age patients and older age patients in any of the treatment groups.

Table 23 Change from Baseline in 6MWD (m) by Demographic Characteristics – Study 876

	Placebo (combined) N=16	3 mg/kg Drisapersen N=17	6 mg/kg Drisapersen N=18
Age ≤ 7			
N	6	8	10
Mean Baseline	445.3	439.1	385.2
Adjusted Mean Change	-13.6	-21.5	17.1
Adjusted diff vs. placebo		-7.9	30.7
Age > 7			
N	10	9	8
Mean Baseline	399.1	393.9	409.9
Adjusted Mean Change	-16.0	-16.1	11.8
Adjusted diff vs. placebo		-0.1	27.8

Source: Reviewer's analysis

4.2 Other Special/Subgroup Populations

The sponsor submitted an Information Amendment on August 31, 2015, in which additional post-hoc analyses were presented. The sponsor stated that combined with the analyses presented in ISE in the original submission, these analyses supported the conclusion that Study 044 included a large proportion of subjects who were older and more impaired at baseline when compared with the populations in the two concurrently conducted phase-2 studies. When removing the older, more progressed subjects from the DMD114044 population, a positive treatment effect in the 3 remaining population subgroups was revealed, all of whom saw a 6MWD treatment benefit similar to or greater than the effects seen in the Phase-2 placebo-controlled studies. Using this analysis, the Phase-3 data could be seen to confirm the efficacy demonstrated in the other randomized Phase-2 studies.

In this Information Amendment, the sponsor made 3 major arguments.

1. Data displays by both age and baseline 6MWD categories (Sponsor's Table 1 below) revealed significant differences in 6MWD trajectory among subgroups, with consistent treatment effect for all subgroups except for the subgroup of older boys with low baseline walking function (age >7 and 6MWD <=330 m). However, although subgroup analyses of treatment effect taking age and baseline 6MWD into account were performed and included in the Phase-3 CSR, the analysis that considered a combination of age group and baseline 6MWD as a covariate was not included in the overall model.
2. Baseline difference between the treatment groups disadvantaged the drisapersen group. As the Phase-3 study was not designed to accommodate these subgroup differences, critical baseline differences occurred in the randomized groups. For example while 46% of placebo-treated subjects were in the young, functionally-able group at baseline, only 26% of drisapersen-treated subjects were in this category.
3. Formal statistical analyses of the residuals from the model fit confirmed a highly skewed data distribution rejecting the MMRM model assumption of normal data distribution ($p<0.0001$), different from what was observe from Phase-2 studies.

Table 24 Table 1 of Sponsor's Information Amendment – Study 044

Table 1: (Table 6 of Module 2.5): Summary of 6MWD change from Baseline to Week 48 by age and baseline categories (DMD114044)

	Age ≤ 7 years				Age > 7 years			
	6MWD ≤ 330 meters		6MWD > 330 meters		6MWD ≤ 330 meters		6MWD > 330 meters	
	6 mg/kg	Placebo	6 mg/kg	Placebo	6 mg/kg	Placebo	6 mg/kg	Placebo
N	17	4	33	25	33	17	34	13
Mean	11.38	-62.38	-11.67	-17.68	-123.63	-107.96	-25.37	-51.87
SD	49.43	98.72	63.24	50.66	93.80	108.27	61.27	69.93
Median	**23.0**	**-53.8**	**-6.60**	**-26.2**	**-109.3**	**-109.5**	**-22.4**	**-55.0**
Min	-108.7	-184.0	-215.0	-96.0	-303.0	-311.0	-194.0	-185.0
Max	68.0	42.0	112.4	105.5	48.2	89.0	102.0	48.0
Difference in Medians	**+76.8**		**+19.8**		**-0.2**		**+32.6**	

Source: DMD114044 CSR Table 2.138 provided in the original NDA (27 April 2015)
Note: Difference refers to difference in 6MWD median for drisapersen-treated subjects compared with placebo

In an post-hoc analysis performed by the sponsor (Table 25 [Table 2 of Information Amendment]), the primary analysis model (MMRM) was enhanced to account for potential subgroup differences by adding the baseline age and baseline 6MWD subgroup (age<=7 & 6MWD<=330, age<=7 & 6MWD>330, age>7 & 6MWD<=330, and age>7 & 6MWD >330) and treatment by age and baseline 6MWD subgroup interaction terms to the MMRM model. This analysis yielded a treatment difference of 20 m (p = 0.118), and confirmed a significant treatment-by-subgroup interaction (p=0.047).

The only subgroup that did not show a treatment benefit was the group of older patients with reduced baseline walking function (age > 7 and 6MWD <= 330m). The enhanced MMRM model generated an average treatment benefit of 33 m with a nominal p-value of 0.012 after excluding this more severe population (Table 25).

To address the issue of non-normal data distribution, the MMRM model adjusting for subgroup difference was further enhanced by standardized rank transformation. This nonparametric analysis model confirmed a highly significant treatment-by-subgroup interaction (p=0.006), and significant treatment effect at Week 48 for the total trial population (p=0.012) (Table 25).

With the non-parametric approach, when the older, more progressed subjects were removed from the analysis, the treatment effect at Week 48 was highly significant (p=0.002). Table 25 summarizes the treatment effect based on MMRM and MMRM-Ranked modeling.

Table 25 Table 2 of Sponsor's Information Amendment – Study 044

Table 2: MMRM and MMRM RANKED Modeling: Summary of Treatment Effect

Model	Population	Placebo (adjusted mean)	6mg/kg (adjusted mean)	Treatment effect vs. Placebo	P-value of Interaction of Treatment and Subgroup	P-value of Treatment Difference	P-value of Interaction of Treatment and Subgroup (Ranked data)	P-value of Treatment Difference (Ranked data)
MMRM	Overall*	-60 m	-40m	+20 m	0.047	0.118	0.006	0.012
MMRM	Overall ** minus older/more severe group	-44 m	-11m	+33 m	0.013	0.012	0.068	0.002

Source Tables: 005_1.pdf, 005_2.pdf, 005_3.pdf, 005_4.pdf, 005_5.pdf, 005_6.pdf, 005_7.pdf, 005_8.pdf

* Overall population includes subgroups: <=7 <=330; <=7 >330; >7 <=330; >7 >330m

** Overall population minus older/more severe group: <=7 <=330; <=7 >330; ~~>7 <=330~~; >7 >330m

Note: p-values included are provided for descriptive purposes

The sponsor concluded that collectively, the post hoc analyses presented in the NDA and supplemented in this document provided additional supportive evidence of clinical benefit similar to what was observed in Phase-2 studies.

Reviewer's Analysis

The results shown in sponsor's Table 1 appeared to show contradictory, or at least inconsistent, results. It showed that in the younger age group, the drug was benefiting the more impaired patients (6MWD <=330) with median treatment difference of 76.8 meters. However, in the older age group, the drug was benefiting less impaired patients (6MWD > 330) with median treatment difference of 32.6.

Putting aside the treatment comparisons, which somewhat relied on how well placebo-treated patients responded, one could simply look at each individual subgroup in the median change from baseline. The median change from baseline for the placebo-treated patients appeared to be consistent with the common belief that patients who were more impaired do worse as shown in both younger age group and older age group (-53.8 vs. -26.2 and -109.5 vs. -55.0, respectively). However, the drisapersen-treated patients again showed contradicting results as in the younger age more impaired patients were doing relatively better (23.0 vs. -6.6) and in the older age more impaired patients were doing worse (-109.3 vs. -22.4). This occurred when all subgroup had at least 17 patients.

In addition, the analysis shown in Table 1 used a specific subgrouping with age cut at 7 years and baseline 6MWD cut at 330 meters. The results presented could be sensitive to the cutoff points chosen. The following table presents a summary using baseline 6MWD cutoff at 320 and 350 meters instead of 330 meters, and leaving everything else the same.

Table 26 A comparison to Sponsor's Table 1 when baseline 6MWD is cut at 320 or at 350 – Study 044

Baseline 6MWD cut at 320	**Age ≤ 7 years**				**Age > 7 years**			
	Group 1 6MWD ≤ 320		**Group 2 6MWD > 320**		**Group 3 6MWD ≤ 320**		**Group 4 6MWD > 320**	
	6 mg/kg	Placebo	6 mg/kg	Placebo	6 mg/kg	Placebo	6 mg/kg	Placebo
N	11	2	39	27	31	15	36	15
Mean	12.4	-139.5	-8.4	-15.3	-129.1	-129.0	-26.1	-38.3
SD	49.8	62.9	61.7	50.0	92.9	95.6	61.2	75.5
Median	**24.9**	**-139.5**	**1.0**	**-26.0**	**-121.0**	**-111.0**	**-22.4**	**-28.5**
Min	-108.7	-184.0	-215.0	-96.0	-303.0	-311.0	-194.0	-185.5
Max	66.0	-95.0	112.4	105.5	48.2	24.0	102.0	89.0
Diff in median	**164.4**		**27.0**		**-10.0**		**6.1**	
Baseline 6MWD cut at 350	**Group 1 6MWD ≤ 350**		**Group 2 6MWD > 350**		**Group 3 6MWD ≤ 350**		**Group 4 6MWD > 350**	
	6 mg/kg	Placebo	6 mg/kg	Placebo	6 mg/kg	Placebo	6 mg/kg	Placebo
N	19	7	31	22	37	20	30	10
Mean	6.1	-44.3	-10.0	-17.3	-115.3	-104.0	-22.6	-42.9
SD	49.2	73.6	64.9	54.0	96.8	100.2	54.8	77.2
Median	**22.0**	**-26.0**	**1.0**	**-27.1**	**-109.0**	**-103.2**	**-22.4**	**-22.1**
Min	-108.7	-184.0	-215.0	-96.0	-303.0	-311.0	-141.0	-185.0
Max	68.0	42.0	112.4	105.5	61.0	89.0	102.0	48.0
Diff in median	**48.0**		**28.1**		**-5.8**		**-0.3**	

Source: Review's analysis

As shown in the above table the benefit seen in the group with age > 7 and 6MWD > 330 m disappeared quickly when the cutoff point of baseline 6MWD changed from 330 to 320 or 350. What the sponsor believed to be a treatment effect could be simply the results of this variability.

Next, let us discuss the analysis model and results using the model with the additional variables of age with baseline 6MWD group and its interaction with the treatment group.

First, the significance of the interaction term of the subgroup (baseline 6MWD and age group) with treatment group (p=0.047) could be an indication of the contradicting directions pointed out above. The reduced p-value from 0.415 in the primary analysis to 0.118 in the sponsor's analysis in Table 2 could be a result of the dominant effect from group 1 (age ≤ 7 and 6MWD ≤ 330) due to its contribution as a group with substantially large treatment difference.

In the primary MMRM analysis, each patient contributed 4 assessments in the repeated measure analysis. However, in the analysis shown in sponsor's Table 2, the contribution from this smallest group of 17 patients created a dominant GROUP effect. If we exclude group 3 (age > 7 and 6MWD ≤ 330) in the analysis, as did the sponsor, an even larger dominant group effect could be the reason of the smaller p-value of 0.012. One could get even smaller p-value by cutting baseline 6MWD at 310 meters instead of 330 meters. In that case, the treatment difference in group 1 would be over 200 meters; not because drisapersen-treated patients did better, but because the only placebo-treated patient left in the group had a change from baseline of -184 meters.

In order to elaborate the above points, let us have more details of the two models presented in the sponsor's Table 2 by comparing the estimates of the coefficients from the models with and without group 3 (age > 7 and 6MWD $\leq$ 330). These estimates represent how much each effect contributed to the estimated treatment difference. The estimates of the coefficients of the group effect are relative to group 4 (age > 7 and 6MWD > 330).

Table 27 Coefficient estimate of the MMRM analysis with/without group 3 presented by sponsor in Table 2 – Study 044

Coefficient estimate relative to Group 4	Group	Estimate	Treatment difference	p-value of interaction group*treatment	p-value of treatment difference
MMRM with Group 3 (row 2 of Table 2)	1	-2.85	20.08	0.047	0.118
	2	35.59			
	3	8.20			
	Group 1*treatment	25.56			
	Group 2*treatment	-32.32			
	Group 3*treatment	-29.18			
MMRM excluding group 3 (row 3 of Table 2)	1	-15.41	32.93	0.013	0.012
	2	34.38			
	Group 1*treatment	32.18			
	Group 2*treatment	-31.56			

Source: Reviewer's analysis

In the above table, there was a substantial change in the effect of group 1 (from -2.85 to -15.41) and group 1 by treatment interaction (from 25.56 to 32.18) when group 3 was excluded. Other effects were little changed. The exclusion of group 3 increased rather than reduced the group by treatment interaction (from 0.047 to 0.013).

The following 2 tables present similar results when baseline 6MWD is cut at 320 meters or 350 meters.

Table 28 Coefficient estimate of the MMRM analysis with/without group 3 where baseline 6MWD is cut at 320 meters – Study 044

Coefficient estimate relative to Group 4	Group	Estimate	Treatment difference	p-value of interaction group*treatment	p-value of treatment difference
MMRM with Group 3 (row 2 of Table 2)	1	-5.11	21.20	0.246	0.126
	2	26.83			
	3	-1.34			
	Group 1*treatment	35.21			
	Group 2*treatment	-21.26			
	Group 3*treatment	-18.25			
MMRM excluding group 3 (row 3 of Table 2)	1	-17.59	30.96	0.074	0.0326
	2	27.59			
	Group 1*treatment	40.68			
	Group 2*treatment	-22.25			

Source: Reviewer's analysis

Table 29 Coefficient estimate of the MMRM analysis with/without group 3 where baseline 6MWD is cut at 350 meters – Study 044

Coefficient estimate relative to Group 4	Group	Estimate	Treatment difference	p-value of interaction group*treatment	p-value of treatment difference
MMRM with Group 3 (row 2 of sponsor's Table 2)	1	23.14	15.57	0.238	0.2153
	2	35.07			
	3	13.33			
	Group 1*treatment	-0.25			
	Group 2*treatment	-32.07			
	Group 3*treatment	-26.96			
MMRM excluding group 3 (row 3 of sponsor's Table 2)	1	11.19	23.42	0.126	0.0621
	2	33.18			
	Group 1*treatment	6.50			
	Group 2*treatment	-30.20			

Source: Reviewer's analysis

I agree that the phase-3 study had the patient population with more impaired patients compared to the phase-2 studies and there seemed to be some disadvantage for the drisapersen group due to randomization. These factors simply made the study difficult to show treatment effect if any, but did not prove that the treatment had an effect.

In addition, in the sponsor's analysis that added the subgroup of age combined with baseline 6MWD as an effect in the MMRM model, the baseline 6MWD was accounted twice. The model included baseline 6MWD, and age with baseline 6MWD combined effect. Such model is inappropriate. We could consider adding age group as an additional factor in the model as a post-hoc analysis. When age group of ≤ 7 years and > 7 years was added to the primary model, the treatment difference is 11.8 m with a nominal p-value of 0.347, similar to the results from the primary analysis.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The 6 mg/kg weekly dosing drisapersen regimen was included in all three efficacy studies. The two small phase-2 studies showed significant or near significant treatment difference while the large phase-3 trial was negative on the primary endpoint.

The positive phase-2 trial 117, though small in size, appeared to have consistent results in sensitivity and post-hoc analyses. The phase-3 trial 044, in contrast, with much larger size showed equally consistent negative results.

An information amendment was submitted in which the sponsor made an argument that the 6 mg/kg drisapersen was effective after excluding the group of patients with older age and more severe disease stage (age > 7 and baseline 6MWD > 330) at entry of the study.

I found that the argument to be weak and not well supported by the data. When the cutoff point of baseline 6MWD in the sponsor's suggested group changed from 330 m to 320 m or 350 m, there was a large swing in the median change of 6MWD in group 1 and treatment difference in group 4 simply disappeared.

5.2 Conclusions and Recommendations

Mixed outcomes with positive results in phase-2 trial 117 and negative results in phase-3 trial 044 have hampered determination whether there was any the treatment.

If another study was to be conducted, a stratified randomization taking into account of difference in age and baseline 6MWD needs to be implemented.

VI. Consultative Review:
MRI Assessments and Measurements

DEPARTMENT OF HEALTH AND HUMAN SERVICES **M E M O R A N D U M**

Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993

Intercenter Consultative Review

ICC1500291 – NDA 206,031

FOR CONSULTED CENTER'S (CDER) USE ONLY

Date: September 11, 2015

To:
Veneeta Tandon, Ph.D.
Ron Farkas, M.D., Ph.D.
CDER/OND/ODEI/DNP

From:
Daniel Krainak, Ph.D.
Gary Levine, M.D.
CDRH/OIR/DRH

RPM: Fannie Choy

Subject: NDA 206,031
KYNDRISA (drisapersen)
BioMarin Pharmceuticals, Inc.

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I. Summary

Quantitative fat fraction by MR is likely to represent underlying tissue content; however, the changes observed in the study are presented from a small subset of patients (often with one or more missing data points) across a variety of vendors. We have greater uncertainty about quantitative T2 measures in the context of edema as T2 may be influenced by many physiologic factors (including inflammation/edema, local bleeding/hematocrit, fat, [fat effects T1 more than T2] and more). Most of the commonly seen pathologies (infection/inflammation, tumor [benign or malignant], etc.) lead to an increase in T2 values. Therefore, an altered T2 is sensitive but not specific unless correctly interpreted in the context of the underlying pathophysiology.

The data presented are unconvincing for several reasons: the small number of subjects with fat fraction data at baseline, 24 weeks and 48 weeks (five control, one at 3/mg/wk and five at 6 mg/kg/wk with data at all three time points), variability in the MR systems used, and lack of data concerning the actual quality control measurements from phantoms. In addition, we recommend careful investigation by statistical experts for this dataset, in particular about whether the sponsor appropriately addressed concerns about multiple comparisons (small number of subjects, multiple treatment groups, multiple muscles, and multiple MR metrics), the small sample size, and potential for sampling bias.

Small changes in quantitative fat fraction MR values were observed between groups that on the order of the expected variability and reproducibility (around 3%) of the technique. The data were presented in terms of the group means, not individual traces, which may be more appropriate given the small sample. Sample plots for individual muscles and patients for rectus femoris and vastus lateralis for individuals with data at all three time points are provided as examples, though other muscles may show slightly different trends.

Studies suggest a relationship between quantitative fat fraction measured by MR and patient function. The magnitude of the changes observed in the study population is on the order of the uncertainty in the measurement technique (approximately 3%). Based on existing literature it is unclear if changes in fat fraction provide of 2.7 – 5.2% in the placebo group (N = 5) compared to 0.9 – 3.8% in the 6 mg/kg/wk group (N = 6) over 48 weeks would be indicative of a functional difference between groups.

Specific questions from the lead reviewer are addressed at the end of this consulting memo.

II. Background

When we initially reviewed the information provided by the sponsor, we determined that there was insufficient information to assess the reliability and quality of the data. In addition, the limited dataset (small number of participants) and relationships of some of the MRI-based quantitative measures (specifically T2 measures) to the parameter(s) of interest (such as edema) were unclear. We interactively requested additional information related to the MRI dataset from DMD114876. The sponsor responded to our inquiry and provided additional supporting information including the image acquisition guidelines and related publications. In this review, we consider the original information and the response to the additional information request provided by the sponsor related to MR imaging in this study.

Name of product

KYNDRISA (drispersen)
BioMarin Pharmaceuticals, Inc,

Intended Use

Treatment of Duchenne muscular dystrophy (DMD) with mutations in the dystrophin gene that are amenable to treatment with exon 51 skipping as determined by genetic testing.

III. Scope of this consultative review

The lead reviewer requested:

> The sponsor suggests that muscle MRI is supportive of efficacy, specifically based on "fat fraction" and "edema". Please provide advice on the reliability and meaningfulness of the effects observed. For example, for this type of MRI measurement, how much confidence is there that the "fat fraction" or "edema" measurements are really representing what they purport to represent – particularly in the setting of use of a drug that might alter physiology from that observed in natural history? Are these types of measures objective and reproducible? Is there a way to put the effect size in the context of potential clinical meaningfulness?

The scope of this review is limited to the use of MRI assessments and measurements in NDA206,031.

IV. Summary of the clinical trial

Of nine clinical studies cited, one included analyzable MRI data:

DMD114876 included a pilot MRI study of six different muscles of the right thigh at various time points (baseline, week 24 - 24 weeks after the start of treatment, week 48 – 24 weeks after last treatment). Normalized T2-weighted and fat fraction signal showed a shift in patients treated with drispersen compared to the placebo subjects:

- T2-weighted signal decreased (-0.07 to -0.23; N = 14) compared to controls (0.07 – 0.14; N = 10)
- Apparent fat fraction increased (2.7 – 5.2%; N = 5) in placebo group compared to 6 mg/kg/wk treatment (0.9 – 3.8%; N = 6).
- Effects persisted up to 24 weeks post-treatment

Study No.	Phase	Study objectives	Study design	Treatment*
Placebo-controlled studies				
DMD114876	II	Efficacy, tolerability, safety, PD, and PK	Double-blind, randomised, placebo-controlled Parallel-dose level groups	24 weeks SC: 6 mg/kg/wk 3 mg/kg/wk placebo 24 week off-treatment follow-up

Table 2: Muscle biopsy (*tibialis anterior*[1]) and biomarker assessments in drisapersen clinical studies

Study No.	Group	Number (N)	Biopsy pre-treatment	Biopsy post-treatment	Biopsy Analysis[2]	Muscle pathology[2]
Placebo-controlled studies						
DMD114876	6mg/kg/wk 3mg/kg/wk Placebo	18 17 16	Yes, all	all: 24wk 3rd biopsy at 12wk or 36wk[3]	DL, ES, DysP	sCK, MRI

From section 5.2.3 of the Mechanism-Based Assessment Of Drisapersen's Clinical Pharmacological

Effects

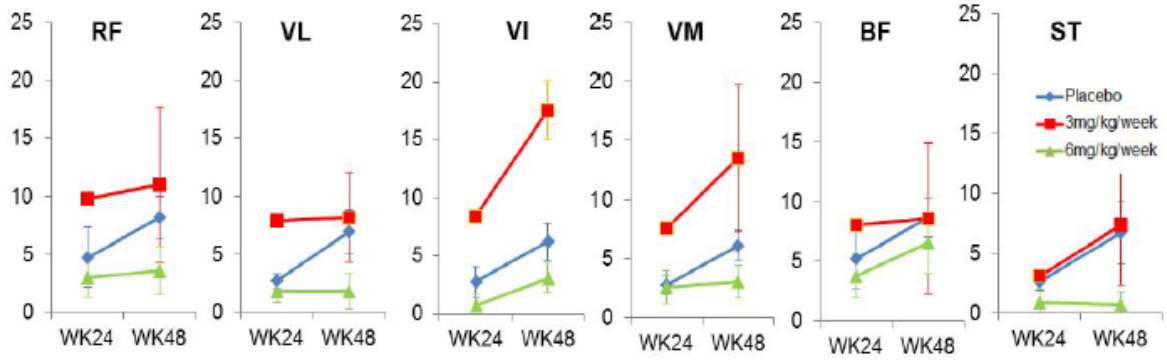

Figure 21: Reduced rate of fat infiltration fraction in subjects receiving 6 mg/kg drisapersen in DMD114876.

Plots showing the apparent fat fraction (y-axis, %) change from baseline (with SE) in each of the muscles for all subjects with evaluable data at each visit.; 6 muscle groups were examined. ; RF: rectus femoris; VL: vastus lateralis; VI: vastus intermedius; VM: vastus medialis; BF: bicep femoris; and ST: semitendinosus. The number of subjects in each of these treatments are as follows, placebo group n=5, 5, 3 mg/kg/week treatment group n=1, 2and 6 mg/kg/week group;n=6, 5 at the Week 24 and Week 48 visit, respectively. Note that the 3mg/kg was only based on n=1 (24wk) and n=2 (48wk) and is therefore not considered to be representative.

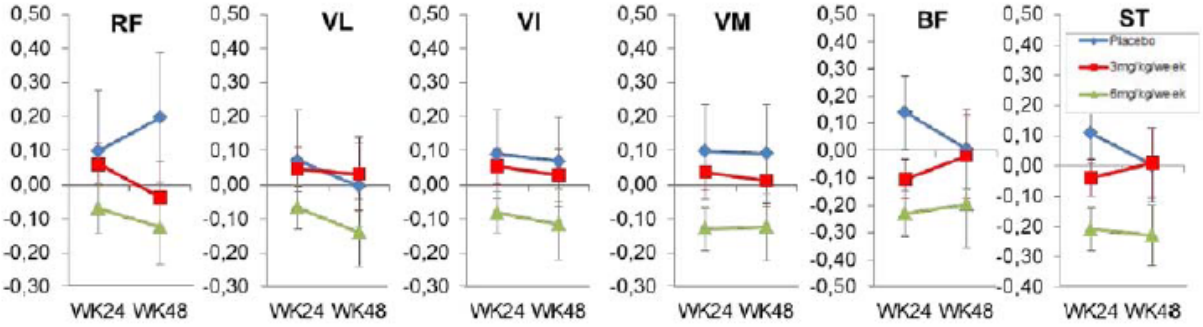

Figure 22: Reduced T2 weighted signal in subjects receiving drisapersen in DMD114876.

Plots (with SE) showing the normalised T2-weighted signal (y-axis,) change from baseline in each of the muscles for all subjects with evaluable data at each visit. All: all subjects; placebo group; 3 mg/kg/week treatment group; 6 mg/kg/week treatment group; RF: rectus femoris; VL: vastus lateralis; VI: vastus intermedius; VM: vastus medialis; BF: bicep femoris; and ST: semitendinosus. The number of subjects in each of these groups, is placebo: n=10, 9; 3 mg/kg/week: n=7, 7; 6 mg/kg/week: n=14, 11, at the Week 24 and Week 48 visit, respectively.

DMD114044 – MRI data were only acquired in a small number of subjects and data were not analyzed due to technology issues at acquisition.

Image Acquisition Guidelines, Protocols, and Quality Control in DMD114876

Consistent with literature recommendations, the sponsor asked all participants to avoid any excessive physical activity beyond their normal levels for at least one week prior to examination. The acquisition protocol required images to be acquired on the same system for the same subject. Quality control assessments were included as part of the study and there was a centralized data repository and analysis site that provided quality checks. However, if data were of insufficient quality (for example, subject motion, deviation from the study protocol, etc.), subjects were not rescanned.

Reviewer comment

The sponsor cites MRI data showing trends for reduction in edema (swelling) and adipose (fatty tissue) replacement signals based on T2 mapping and fat fraction methodology. However, the data presented are unconvincing for multiple reasons. Both quantitative fat fraction and T2-mapping techniques may be performed in multiple ways and the methodology used or variability in the methodology may impact the accuracy and uncertainty associated with the measurement. The sponsor notes that multiple MR system vendors were used including GE, Siemens, and Philips. There may be differences between vendors or models even when attempting to control differences between manufacturers.

Validation for the quantitative techniques (fat fraction or T2 mapping) used in the study was presented primarily as literature references wand supplemental articles were used to determine validation of these techniques. See sections below on the techniques and reproducibility.

While quantitative fat fraction is a logical extension of qualitative assessment of fatty infiltration as a measure of changing fat content in tissue, the relevancy and meaningfulness of changes in T2 values are less obvious. T2 may be changed by multiple factors and the relationship between the disease process and T2 change is not adequately presented. Much of the literature related to MR measurements in this patient population is recent, performed by a small number of groups using a variety of methods in small numbers of participants, and occasionally with mixed results. More justification for the relevancy of T2 mapping as related to the disease would be needed to understand the relationship of T2 to DMD and treatments.

If the data are further considered, we recommend careful investigation from a statistical expert as the limited number of individuals, multiple muscles, and multiple metrics for comparison were noted, but the method for controlling for multiple comparisons was unclear. Also, the same number of individuals was not scanned at all three time points (baseline, week 24, and week 48) and the missing data should be appropriately accounted for.

V. Description of MR techniques for evaluating fat fraction and edema

Fat Fraction

Fat fraction techniques (often referred to as DIXON-method techniques) are often used in the liver to produce qualitative and potentially quantitative fat fraction images that show the difference between water and triglyceride fat fraction. The Dixon technique typically uses gradient recalled echo (GRE) MR images from two or three echo times (TEs) known as the in-phase (IP) and out-of-phase (OP) or opposed phase. The IP image is the sum of water and fat, the OP is the difference between the water and fat. From these images, the fat/water proton ratio may be determined.

Based on the phantom and repeatability studies provided to support premarket notifications for these types of techniques, including (note that this list is not exhaustive):

K122035 – Resonant Health Services - Hepafat
K103411 – GE Medical Systems – IDEAL-IQ
K133526 – Philips Medical Systems - mDIXON-Quant

All of the 510(k)-cleared quantitative Dixon-based fat fraction methods have been restricted to the liver. Variability (scanner-to-scanner reproducibility) is in the range of 3-11% in phantoms or in vivo (95% limit of agreement). Interanalyst 95% confidence intervals were around 1.5% for volumetric liver measurements of fat fraction. Some sponsors provided evidence to support ± 3 - 3.5% reproducibility claims. Correlation to pathology was provided for a subset of the submissions. However, please note that the applications cleared (510[k]) to date have been in the liver whereas the current application uses the technique in leg muscle tissue. Also, note there may be significant image acquisition differences between vendors, for example, Philips mDIXON technique uses a six-echo pulse sequence instead of the traditional two-point method.

The data provided and previous articles suggest large muscle-to-muscle variability. Gaeta and others (2012) observed a range of fat fraction values in 20 boys with DMD from mean of 46.3% in the gluteus maximums to a mean of 2.7% in the gracilis. Morrow and others (2014) found significant differences between muscles in adults, with small absolute differences with mean fat fractions in the 0.6 – 2.6% range and limits of agreement for individual regions of interest ranging from -1.25 to 1.01% (thigh) and -1.55 to 0.95% (calf) across all muscles examined (rectus femoris, vastus lateralis, vastus intermedius, vastus medialis, semimembranosus, semitendinosus, biceps femoris, adductor magnus, sartorius, gracilis, tibialis anterior, peroneus longus, lateral gastrocnemius, medial gastrocnemius, soleus and tibialis posterior muscles). Overall, the study population in Morrow and others (2014) had very low fat fraction values (highest value less than 16% with average values less than 3%) across all volunteers (n = 47) and muscles, which is not representative of the values typically found in DMD patients. Notably, single site studies such as Morrow and others (2014) may have smaller uncertainty.

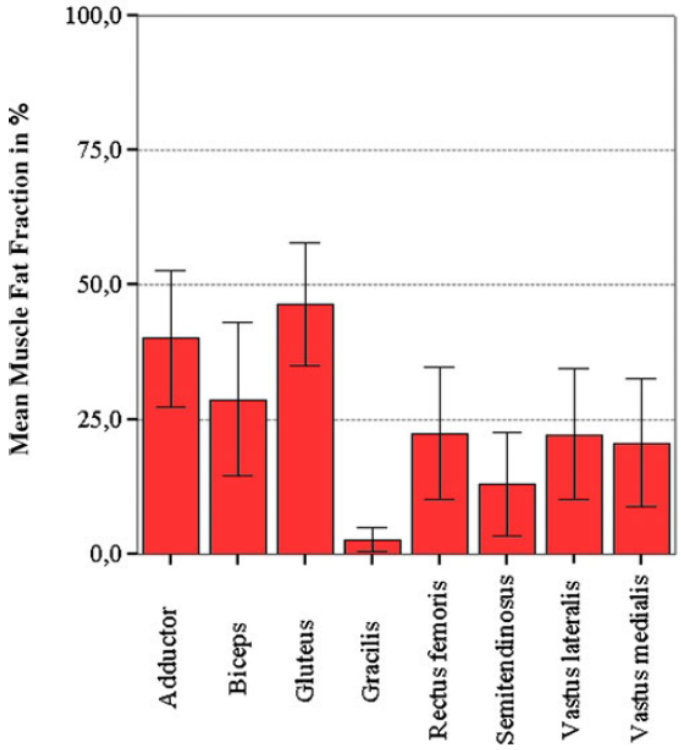

Fig. 1 Bar chart shows mean muscle fat fraction (MFF ± SD) of eight muscles in 20 patients. The gluteus maximus muscle has the highest mean MFF and the gracilis muscle has the lowest

Figure from Gaeta and others 2012

As an example from the study DMD114876, for subject 28 at randomization

Rectus femoris right	27.66
Vastus lateralis right	21.15
Vastus intermedius right	15.74
Vastus medialis right	14.41
Biceps femoris right	38.53
Semitendinosus right	18.06

Spatial heterogeneity in the fat fraction may also be observed within and between dystrophic muscles and even in muscles with similar fat fraction values.

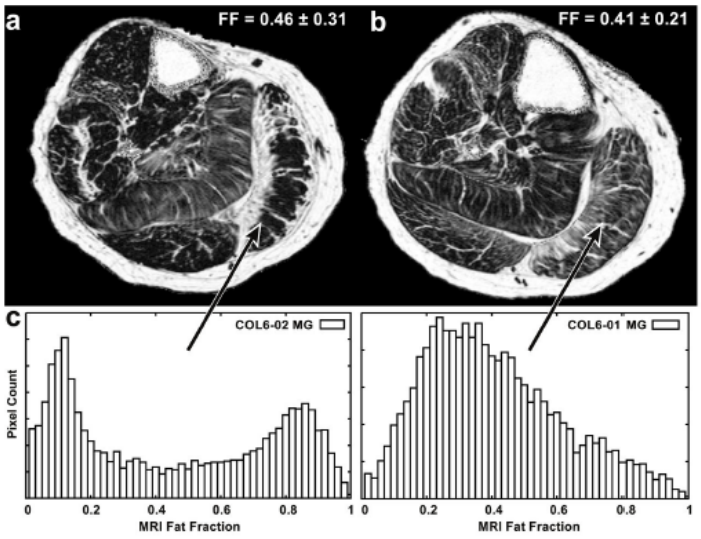

Figure 7.
Examples of histograms from the medial gastrocnemius of two different COL6 subjects with similar fat fraction as measured by MRI. Subject (a) showed fatty infiltration inward from the external fascia, which was associated with a bimodal fat fraction distribution (c), whereas subject (b) showed a unimodal distribution characteristic of a more diffuse pattern of fat infiltration.

Figure from Triplett and others (2014) High spatial heterogeneity within muscles was observed within dystrophic muscles.

The reproducibility of fat fraction measures:

Based on the evidence provided for liver, quantitative fat fraction measures based on MRI, when carefully performed are objective measurements and have reproducibility measures which may be approximately 3-5% when carefully conducted. The sponsor provided several references related to the reproducibility of quantitative fat fraction in muscle.

Ponrartana and others (2014) looked at repeatability of quantitative fat fraction in seven healthy children at a single site, single MR system (Philips) using Philips mDIXON protocol in a “coffee-break” experiment (that is scan – reposition the patient – scan within a short time-frame, same session). Mean muscle fat fraction was less than 13% for all individuals and all muscles (gluteus maximus, rectus femoris, vastus medialis, lateralis, and intermedius, semimembranosus, semitendinosus, biceps femoris, combined adductors, anterior and posterior tibialis, peroneus longus, gastrocnemius, and soleus). Triplett and others (2014) observed day-to-day variability in fat fraction of CV = 12% in control muscle (n = 6) and CV = 5.3% in DMD (n = 26) in children based on a two-day repeatability study. Philips 3T system was used for image acquisition in this study. Forbes and others (2013) compared reproducibility of three centers (two with 3T Siemens systems and one with 3T Philips system) using two-compartment coaxial phantoms, but fat fraction reproducibility was not examined using this phantom. Two healthy adults (ages 35 and 42) were examined at all three centers to look at within-subject variation in the soleus and the mean within-subject CV was 7.2 ± 1.3% across centers using an MRS technique to determine lipid fraction. Bonati and others (2015) recently described using quantitative MRI in DMD to achieve reproducibility for quantitative fat fraction of 0.9% in a single scanner, single site study. Morrow and others (2014) examined muscles in 47 adults using MR techniques with 15 adults undergoing repeat examinations two weeks apart and found limits of agreement -1.55 to 1.01% in adults with low fat fraction values.

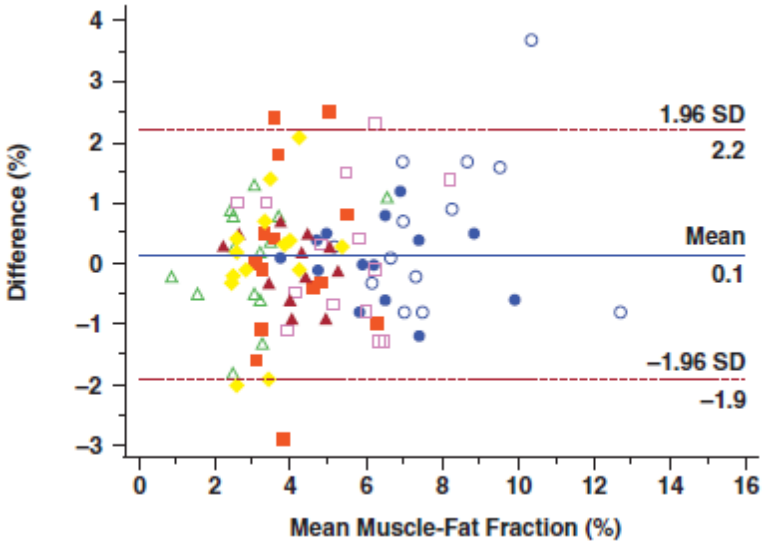

Figure from Ponrartana and other 2014 showing the Bland-Altman plot for a coffee-break test-retest experiment of seven healthy children. Each symbol represents different subject, and each data point represents mean value from each individual muscle measured. The largest difference between two tests was 3.7%.

Thus, reproducibility results across studies may vary and well-controlled studies may achieve better reproducibility.

Histopathology validation of fat fraction

Gaeta and others (2011) compared muscle fat fraction measured by the two-point Dixon technique with muscle biopsy as the reference standard in 27 patients with neuromuscular disorders ages 7 – 67. Six individuals had DMD. Results showed mean differences -0.3 ± 1.3% for mean fat fraction values of around 20% (range 3 – 46%) with limits of agreement ranging from -2.8% to 2.2%.

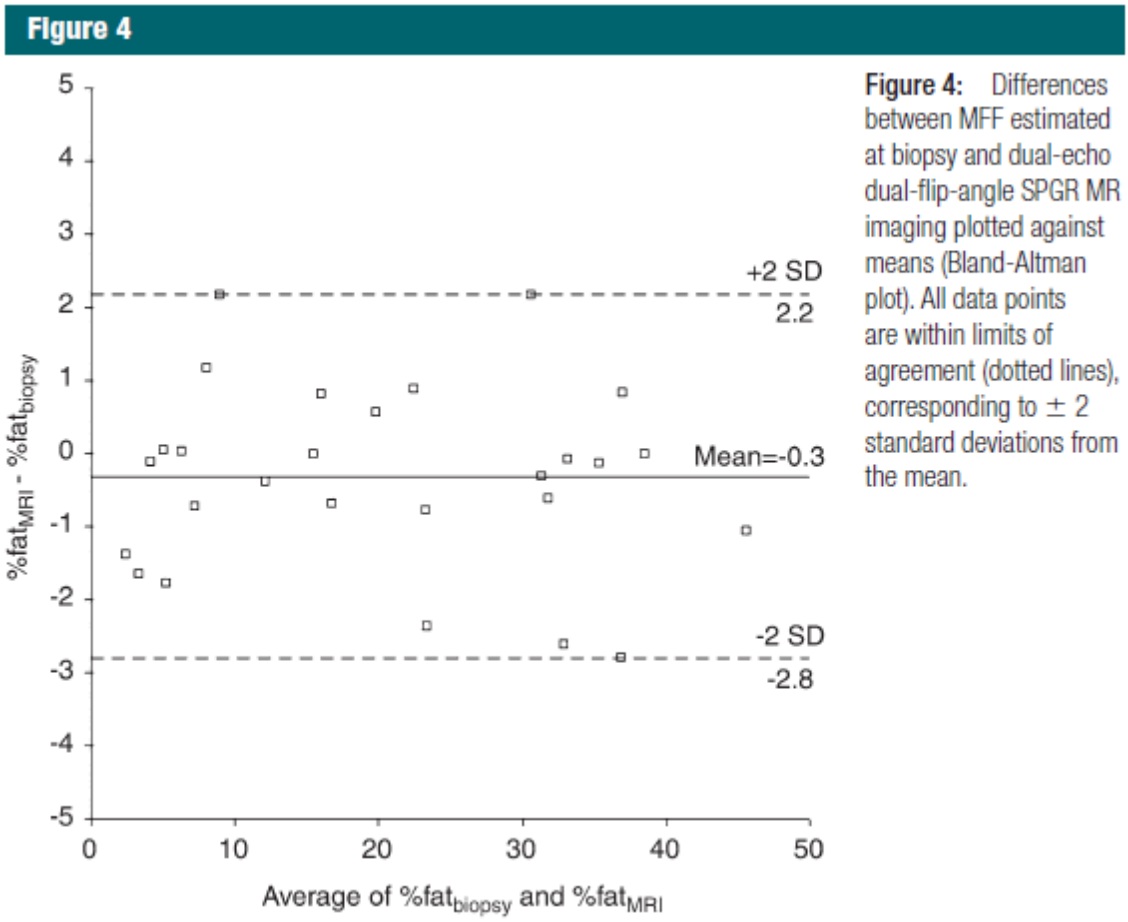

Figure 4: Differences between MFF estimated at biopsy and dual-echo dual-flip-angle SPGR MR imaging plotted against means (Bland-Altman plot). All data points are within limits of agreement (dotted lines), corresponding to ± 2 standard deviations from the mean.

Figure from Gaeta and others (2011) comparing two-point Dixon fat fraction measurements with biopsy.

T2 relaxation & edema

T2 is a magnetic resonance property described as the transverse or spin-spin relaxation and specific pulse sequences may be used to evaluate this property in tissue. Often data are acquired at multiple echo times and modeled as a single exponential function to determine T2 for the voxel or region of interest. T2 measurement by MRI can be accurate and reproducible, but the reliability of the data depends on the technique used.

Measurements of T2 relaxation times are also influenced by fat content as shown in this table from Arpan and others (2013) comparing non-fatsat and fatsat T2-relaxation time. Note the larger differences between techniques in DMD compared to controls. While fat content is not the sole contributor to T2 signal changes, fat content does impact T2 relaxation times. The authors also note that T2 measure obtained from non-fatsat images showed better correlations with functional measures in comparison with those obtained from fatsat. These authors also observed increased heterogeneity in T2 measurements of DMD compared to controls.

Table 2. T_2 relaxation times (ms) for non-fat-saturated (non-fatsat) and fat-saturated (fatsat) images of controls and subjects with Duchenne muscular dystrophy (DMD)

Muscle	Non-fatsat		Fatsat	
	Control	DMD	Control	DMD
SOL	40.3 ± 1.1	50.6 ± 5.5[a]	38.2 ± 0.8	45.3 ± 3.8[a]
MG	39.2 ± 1.9	50.8 ± 7.9[a]	37.1 ± 0.5	45.2 ± 4.3[a]
PER	39.7 ± 1.5	51.2 ± 8.4[a]	37.3 ± 0.6	44.2 ± 3.9[a]
TA	38.7 ± 1.3	45.7 ± 5.0[a]	37.3 ± 1.2	41.5 ± 1.6[a]

MG, medial gastrocnemius; PER, peroneal; SOL, soleus; TA, tibialis anterior.
Values are expressed as mean ± standard deviation (SD).
[a]Significantly different between groups ($p \leq 0.001$)

The relationship between edema and T2 values is unclear. Typically, a fluid sensitive technique (such as STIR or FLAIR) would be used to assess localized increases in signal intensity (for example, bright areas) that would be indicative of inflammation or edema. Quantitative T2 measures may be influenced by physiologic factors other than edema and fat such as iron content, hematocrit, inflammation, fibrosis, or tissue structure alteration. T2 values may also be influenced by steroid use. Therefore, the interpretability of changes in T2 relaxometry values is unclear.

The reproducibility of T2 measures:

Forbes and others (2013) found day-to-day variability T2 w/o fat saturation in medial gastrocnemius, peroneus longus and peroneus brevis, soleus, tibialis anterior, long head of the biceps femoris, gracilis, semetendinosus, and vastulis lateralis (two day study using the same MR system) mean coefficient of variability (CV) ranged 1.3 – 5.9% in ~10 age-matched controls and 1.7 – 5.6% in 25 – 30 boys with DMD where CV = std(repeated measure)/mean(repeated measure).

VI. Example data for fat fraction in two muscles from DMD114876

Given the large patient-to-patient variability and how the sponsor provided the results, two muscles were selected from the sponsor's dataset to examine the trends across time (rectus femoris and vastus lateralis). Statistical comment would be appropriate as there are concerns about the small number of individuals with data points at 0, 24, and 48 weeks as well as that six muscles were examined. Data included in this subset of five placebo, one 3 mg/kg/wk and five 6 mg/kg/wk were from Siemens and GE scanners across a variety of models and at both 1.5T and 3T. There was very limited data demonstrating reproducibility over time in the same patient and even less demonstrating that measurements across MR system manufacturer, field strength, model, and software version provided similar results.

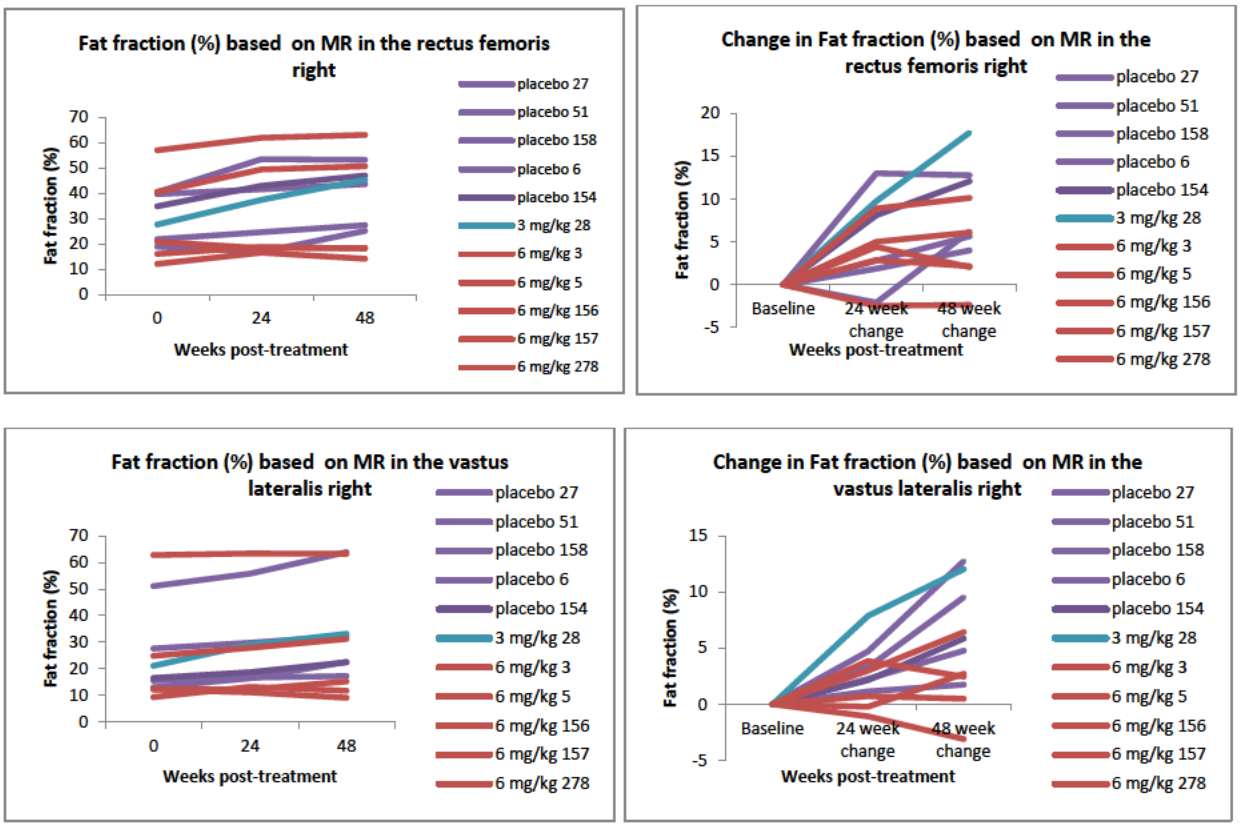

Figure: Two example muscles (rectus femoris [upper row] and vastus lateralis [lower row]) showing individual's data across all three time points as raw values (left column) and change (right column).

The limited data show substantial overlap between treatment groups, large variability by muscle and a wide range of fat fraction observed at baseline.

VII. Response to specific questions from the consultant

Please provide advice on the reliability and meaningfulness of the effects observed. *Response was separated include the potential reliability and meaningfulness.*

1. For example, for this type of MRI measurement, how much confidence is there that the "fat fraction" or "edema" measurements are really representing what they purport to represent – particularly in the setting of use of a drug that might alter physiology from that observed in natural history? Are these types of measures objective and reproducible?

Fat fraction may be evaluated through visual qualitative assessment or quantitative fat fraction techniques. Visual assessment was performed in the DMD1411876 study using the Mercuri scale. Finanger and others (2012) in a review of MR techniques in DMD note:

> "Mercuri et al developed a fourpoint grading system to categorize disease severity, based on visual inspection of fatty tissue infiltration (Mercuri et al., 2002; Mercuri et al., 2005). This strategy was recently used to screen DMD subjects in a clinical trial involving injection with antisense oligonucleotides (van Deutekom et al., 2007). However, there is considerable interest in utilizing quantitative imaging to monitor disease progression and efficacy of treatment strategies, which is the focus of the remainder of this article."

Visual inspection techniques such as the Mercuri scale may have intra- and inter-reader variability and are typically less sensitive to small changes than quantitative techniques (especially those such as quantitative fat fraction that have relatively reliable performance). Therefore, we (like Finanger and others [2012]) have focused on the quantitative fat fraction in our review.

See above for an explanation of the Dixon technique to measure fat fraction. Reproducibility could be considered to be roughly about 3-11% (with well-controlled image acquisition and analysis) depending on the exact technique used. The use of multiple vendors and field strengths without head-to-head reproducibility data for the systems precludes the ability to estimate the uncertainty exactly. Also, validation and reproducibility data referenced in literature was often for different muscles than those in the study and in patients with varying functional characteristics (such as ambulatory and non-ambulatory), and therefore, it is challenging to precisely estimate the uncertainty for the current study. However, the image acquisition protocol in DMD114876 ensured that subjects were scanned on the same scanner with the same software version at all time-points, which should reduce within-subject variance. Data were centrally analyzed and the use of quantitative fat fractions techniques increases the confidence in the limited data provided.

Changes in fat fraction based on quantitative Dixon-methods are likely to reflect true changes in the fat content in muscle; however, the description of the technique in the current study is insufficient to determine if the methodology was adequately controlled and validated to detect changes in magnitude <5%. Quantitative fat fraction methods may be accurate and reproducible when carefully controlled (uncertainty from the method alone may be less than 3% based on evidence provided for commercial products intended for use in the liver as well as other references and possibly less than 1% if carefully controlled). Quantitative fat fraction by MR can be considered a logical progression and substantial improvement from subjective assessment of fatty infiltration by MR.

The meaningfulness of the effects observed for changes in quantitative fat fraction would have to be considered in the correlation to changes in the fat fraction with any other clinical outcomes investigated to date. See response to question 2 below.

More evidence would have to be provided to suggest T2 measurements and T2 signal intensity measures as representative of edema. T2 measurements and changes in T2 may reflect muscle damage, edema, fibrosis, inflammation, fatty inflammation (Arpan et al. 2013; Willcocks et al. 2014), as well as other factors (for example, iron, hematocrit, or exercise). Willcocks and others (2014) provide limited supporting evidence that changes in T2 signal are correlated with functional measures based on a small study (16 boys with DMD; 15 controls) in muscles (soleus, peroneal, tibialis anterior) different than those used in the current study (rectus femoris, vastus lateralis, vastus intermedius, vastus medialis, bicep femoris, semitendinosus). However, Willcocks and others (2014) contrasts previous results from Kim and others (2010) who presented mixed results about changes in T2 values in the gluteus muscles in 11 boys with DMD over time with steroid treatment.

2. Is there a way to put the effect size in the context of potential clinical meaningfulness?

Based on a small literature search, most of the evidence for correlating MR findings to clinical outcomes is relatively recent and conducted in small studies. There is some limited supporting literature in the form of small studies for fat fraction measurements by MR correlating with functional outcomes in DMD (for examples, see Bonati and others 2015; Gaeta and others 2012; Wren and others 2007) but the results vary in MR technique, muscles analyzed, and clinical outcome measures.

Fischmann and others (2013) examined the relationship between motor function measurement (MFM) and fat fraction (based on the 2-pt DIXON technique – Siemens 3T) and found a correlation between fat fraction and a few muscle groups (left and right quadriceps, left and right hamstrings, and left and right adductors).The study (Fischmann and other 2013) included both ambulatory and non-ambulatory patients and examined loss of ambulation and motor function compared with fat fraction measured by MRI. They propose that a change of fat content of 2% should be detectable after six months and that fat fraction

could be used to predict loss in ambulation; however a longitudinal study would be necessary to validate this or any similar model.

Gaeta and others (2012) reported on preliminary experience with fat-fraction and correlation with clinical assessments. Twenty (20) ambulatory boys with DMD were scanned with a 1.5T Philips MR system using a 2-point DIXON method. Analyzed muscles included: gluteus maximus, adductor magnus, rectus femoris, vastus lateralis, vastus medialis, biceps femoris, semitendinosus, and gracilis. In the discussion, they note that "an increase of 20% in MFF (muscle fat fraction) is associated with a high risk of functional reduction" after finding correlations between fat fraction and functional measures (Medical Research Council score [MRCS], timed Gower score, and time to run 10 meters).

Thus, based on existing literature, it is unclear if changes in fat fraction provide of 2.7 – 5.2% in the placebo group (N = 5) compared to 0.9 – 3.8% in the 6 mg/kg/wk group (N = 6) over 48 weeks would be indicative of a functional difference between groups.

VIII. Previous additional information request

We requested additional information interactively (sent to the sponsor August 6, 2015 and response received on August 17, 2015).

You have provided MRI data related to DMD114876. We are concerned about the data quality of the MR-based information as the acquisition and analysis methods may impact the results.

a. Please provide the complete Image Acquisition Guidelines (IAG) documentation. Please be certain to include a detailed description of the acquisition including descriptions of the pulse sequence, critical parameters (such as TE, TR, voxel size, etc.), and note any differences in acquisition between MR system manufacturers or models used in the study. Please describe your procedure for image acquisition quality control and justify why any differences in image acquisition parameters between patients or visits would not impact the results. Please highlight any protocol deviations.
b. Please describe the image analysis procedures including any analysis quality control activities. Please clarify the outputs from your analysis (for example, quantitative fat fraction, T2 relaxation time, T2 signal intensity, etc.).
c. Please provide the quantitative values for each participant by muscle for each visit. Please note any missing data.
d. Please provide an assessment of repeatability, reproducibility and uncertainty for the quantitative techniques (fat fraction and T2 relaxation time) used in the study.

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X. Acknowledgement of supervisory concurrence

Digital Signature Concurrence Table	
Reviewer Sign-Off Daniel Krainak	
Medical Officer Sign-Off Gary Levine, M.D.	
Division Sign-Off	

VII. Clinical Pharmacology Review:

Clinical Pharmacology, Pharmacometrics and Genomics

CLINICAL PHARMACOLOGY REVIEW

NDA Number:	206031
Applicant Name:	BioMarin Pharmaceutical Inc.
Submission Dates:	April 27, 2015; Aug 24, 2015; Aug 28, 2015; Aug 31, 2015;
Brand Name:	Unknown
Generic Name	Drisapersen
Dosage Form:	Single-use clear glass vials containing 200 mg/mL of drisapersen sodium (0.5 mL and 0.8 mL deliverable volume) dissolved in aqueous phosphate buffer
Dosage Strengths:	200 mg/mL
Proposed Indication:	For the treatment of Duchenne muscular dystrophy (DMD) with mutations in the dystrophin gene that are amenable to treatment with exon 51 skipping as determined by genetic testing
OCP Division (s):	DCP 1, DPM, Genomics and Targeted Therapy
Primary Reviewers:	Atul Bhattaram, Bei Yu, Bart Rogers
Team Leaders:	Kevin Krudys, Angela Men, Christian Grimstein

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1 EXECUTIVE SUMMARY

Biomarin is seeking approval for drisapersen for the treatment of Duchenne muscular dystrophy (DMD) in patients with mutations in the dystrophin gene that are amenable to treatment with exon 51 skipping as determined by genetic testing. Drisapersen is an exon skipping oligonucleotide designed to restore the mRNA reading frame and subsequently produce an internally-deleted dystrophin protein. The proposed treatment regimen is to initiate patients with a drisapersen dose of 6 mg/kg twice weekly for the first 3 weeks of treatment. Subsequently, drisapersen is to be administered 6 mg/kg once weekly. It is recommended that drisapersen be administered subcutaneously. Injection sites should be rotated.

The efficacy and safety of drisapersen was evaluated in 2 placebo-controlled clinical studies that had a duration of 48 weeks and 1 placebo-controlled clinical study that had a duration of 24 weeks. In addition, findings from a long term open-label study (up to 168 weeks) were compared to a natural history cohort and were submitted as supportive evidence of effectiveness. The sponsor submitted results of 7 clinical studies to characterize the PK of drisapersen in DMD patients.

The primary purpose of this review from the perspective of the Office of Clinical Pharmacology was to evaluate the sponsor's comparison of findings from the open-label 3 year clinical study (DMD114673) with the sponsor's natural history data.

The findings from the Office of Clinical Pharmacology are as follows:

- Potential issues with the matching analyses comparing the effect of drisapersen on 6 minute walk distance (6MWD) in study DMD114673 with natural history controls were identified. In this study, 12 patients were treated with 6 mg/kg drisapersen for 168 weeks. Drisapersen treated patients were matched with natural history controls on the basis of age and 6MWD. The analysis, according to sponsor, showed improvement in 6MWD in some patients when compared to their matched controls. However, the matching analysis was conducted using one natural history database and did not take into consideration other important prognostic factors such as genetic mutations and rise time. Due to these issues, it is difficult to make any definitive conclusions regarding efficacy of long term treatment with drisapersen.
- Drisapersen was able to lower serum creatine kinase (CK) across all clinical studies. No clear association between changes in serum CK levels and 6 minute walk distance was observed. Changes in serum CK likely reflect pharmacodynamic activity of drisapersen.
- Drisapersen plasma concentrations, after several weeks of treatment, were similar in all clinical efficacy trials (DMD114117, DMD11876 and DMD114044) irrespective of the observed effect on 6MWD.
- The impact of drisapersen binding antibodies and antidystrophin antibodies on efficacy and safety was inconclusive.

- No significant QT prolongation was observed in a clinical efficacy study (DMD 114876).

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the submission (NDA 206031). The review concludes that:

- The long term study DMD114673 does not provide supportive evidence of effectiveness for drisapersen at this time.
- The findings regarding changes in serum CK following drisapersen treatment likely represent a pharmacodynamic effect of drisapersen, however they are not correlated with clinical benefit.
- If found to be safe and effective, drisapersen should be indicated for all mutations amenable to exon-51 skipping.
- There is inadequate information on the effects of drisapersen in patients younger than 5 years of age and not concomitantly treated with corticosteroids. The sponsor should conduct a controlled clinical trial to evaluate drisapersen in this age group.
- The impact of anti-drisapersen antibodies on clinical efficacy and safety should be evaluated in a long term study (> 48 weeks), e.g., the immunogenicity could be assessed in an ongoing study DMD114673.

1.2 Phase 4 Commitments

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The current submission consisted of 7 clinical studies to characterize single and multiple dose-PK of drisapersen in DMD patients between doses of 0.5 mg/kg/week and 9 mg/kg/week (for 9 mg/kg dose level, only single dose PK was evaluated).

Following multiple doses of 3-6 mg/kg/week subcutaneously, the median Tmax is between 2 and 4 hours; the inter-subject variability (% CV) was low to moderate (22-46% for Cmax and 25-47% for AUC0-t). There is a trend of dose proportionality between 3 mg/kg/week and 6 mg/kg/week.

Plasma trough levels and muscle tissue levels increased over time with once weekly dosing and approached steady state after 24 weeks. Drug accumulation in plasma and muscle was observed following multiple doses of drisapersen at 6 mg/kg/week.

Drisapersen is highly bound to human plasma protein in vitro (≥ 98.2%). Unchanged (parent) drisapersen was the major circulating drug-related component detected in the plasma. Drisapersen is not expected to be a substrate of CYP450, and it's not an inhibitor or inducer of major CYP450 isozymes at the therapeutic dose in vitro. Drisapersen and its shortened metabolites are excreted primarily in urine.

Findings from three clinical studies (DMD114117, DMD114876, DMD114044) were used to provide information on benefit/risk ratio of drisapersen. In addition, findings from an open label, longterm study (168 weeks) were compared to subjects from a natural history cohort to provide supportive evidence of effectiveness. Information on biomarkers such as dystrophin and creatine kinase were collected in various studies.

Effect of drisapersen on primary clinical endpoint

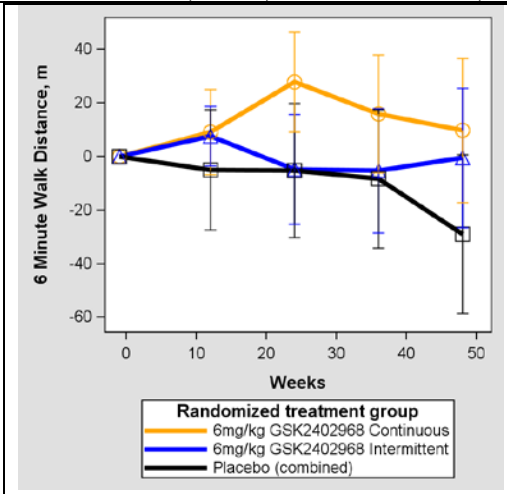
DMD usually first manifests in boys 3 to 7 years of age when they are noted to develop proximal muscle weakness. By 10 to 14 years of age, most boys with DMD have transitioned to full-time wheelchair use [Craig M McDonald et al, Muscle & Nerve, 2010]. Drisapersen was evaluated for its effect on 6 minute walk distance (6MWD) as the primary endpoint. A decline of approximately 30 meters from an average performance on the 6MWD in DMD to a threshold 6MWD of 325 meters or 55%-predicted would place a patient with at risk for more precipitous decline in ambulatory function over the subsequent year [Craig M McDonald et al, Muscle & Nerve, 2013].

Sponsor conducted studies that evaluated dose-response and impact of continuous versus intermittent dosing regimens and enrolled patients with a wide range of baseline prognostic factors known to influence DMD disease progression. Briefly, study DMD114876 evaluated efficacy and safety of 3 and 6 mg/kg doses of drisapersen every week. Study DMD114117 evaluated efficacy and safety of a 6 mg/kg dose of drisaperen administered as a continuous regimen (every week) or as an intermittent regimen (6 mg/kg drisapersen twice weekly on the 1st, 3rd and 5th weeks, once weekly on the 2nd,

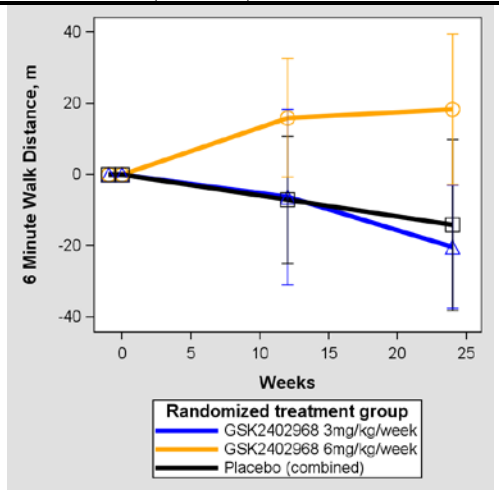
4th and 6th weeks, and no active drug on the 7th to 10th weeks of each 10 week cycle). All subjects in study DMD114117 were initially administered doses twice weekly for the first three weeks (loading dose). The intermittent regimen cycle started after completion of the loading dose regimen. Study DMD114044 studied the effect of 6 mg/kg dose of drisapersen administered weekly. No loading doses were administered in study DMD114044.

Figure 1 shows the mean change in 6MWD across studies in ITT population. Patients in DMD114876 study treated with drisapersen 6 mg/kg relative to placebo showed a change of +27 m at 24 weeks (p=0.0609). Patients in DMD114117 study treated with drisapersen 6 mg/kg relative to placebo showed a change of +35 m at 25 (p=0.0104) and 49 (p=0.0501) weeks relative to placebo. Patients in DMD114044 study treated with drisapersen relative to placebo showed a change of +10 m (p=0.415) at the end of 48 weeks. For further details about clinical significance of the changes in 6MWD and other secondary endpoints, please refer to the review by Dr Veneeta Tandon (Medical Officer, DNP).

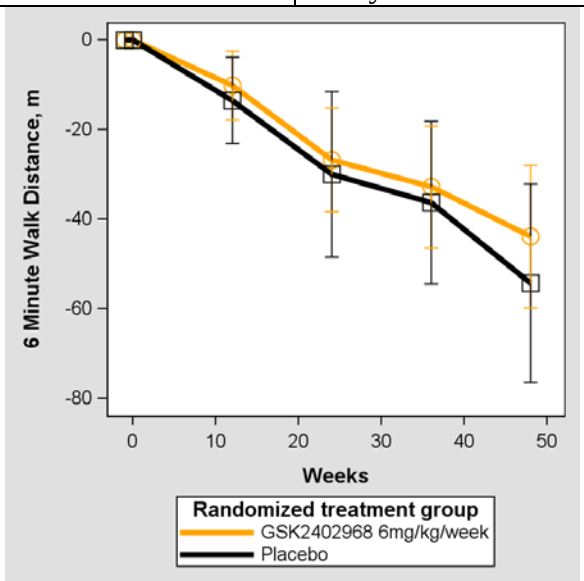
Figure 1. Mean Change from Baseline (95% CI) in 6MWD (m) Population in Studies DMD114117 (N=53), DMD114876 (N=51), DMD114044 (N=162).



Study DMD114117



Study DMD114876



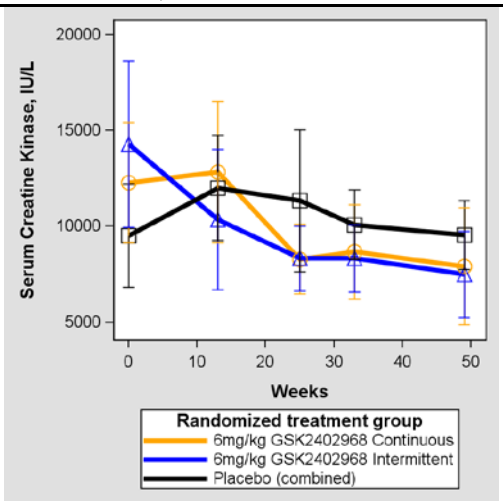
Study DMD114044

Findings from long term study DMD 114673 (N=12) were compared with a natural history control. Patients in the natural history control were on a stable dose of corticosteroids. While matching analyses suggested that some patients have better walking ability than matched controls it should be noted that the matching analyses included mutations not amenable to exon 51 skipping therapy. It is not clear how to evaluate impact of other factors such as supportive care in matching analyses. While improvements in 6MWD in some DMD114673 study patients could be due to drisapersen, definitive treatment benefit upon long term administration of drisapersen cannot be adequately quantified with the available data.

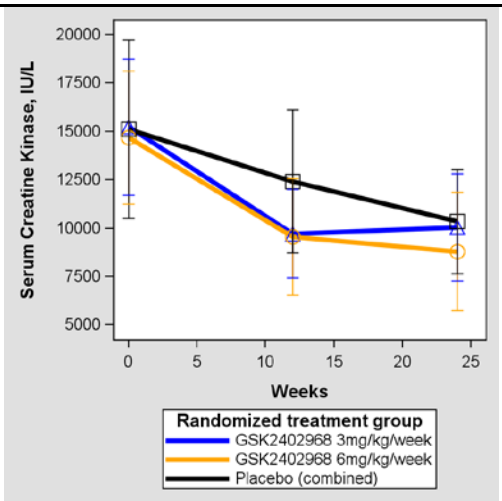
Effect of drisapersen on biomarker (creatine kinase)

Serum creatine kinase is a marker of muscle damage in DMD. Patients with DMD have high levels of creatine kinase (Figure 2). Normal values from healthy subjects are in the range of 60 to 174 IU/L. Drisapersen decreased creatine kinase levels by 30-40% across studies. While serum CK decreases were observed in DMD114044 study, there were no significant findings on the primary endpoint of 6MWD. For further details refer to the review by Dr Veneeta Tandon (Medical Officer, DNP)

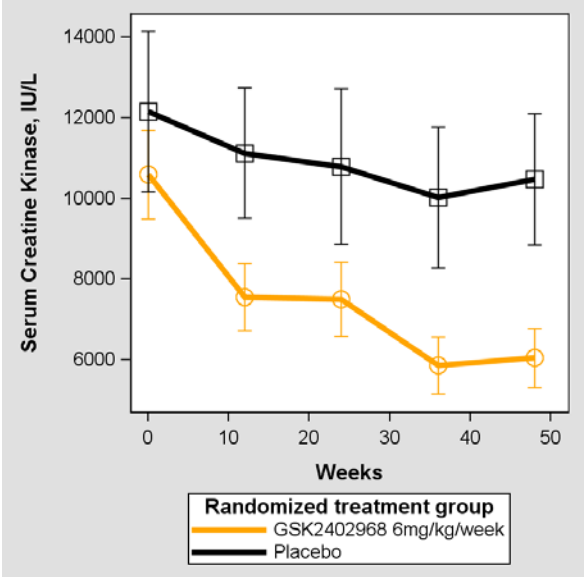
Figure 2. Mean Change in Creatine kinase (95% CI) in Studies DMD114117, DMD114876, DMD114044.



Study DMD114117



Study DMD114876



Study DMD114044

Safety Findings

The adverse events (AEs) of interest are injection site reactions, thrombocytopenia and glomerular nephritis. Table 1 shows overview of on-treatment adverse events in Study DMD114044.

Table 1. Overview of On-Treatment Adverse Events (Safety Population)

	Number (%) of Subjects		
	Placebo (N=61)	Drisapersen 6 mg/kg/week (N=125)	Total (N=186)
Any AE of special interest	37 (61)	114 (91)	151 (81)
Injection site reaction	10 (16)	97 (78)	107 (58)
Renal effects	20 (33)	80 (64)	100 (54)
Inflammation	16 (26)	33 (26)	49 (26)
Coagulation	9 (15)	9 (7)	18 (10)
Hepatic effects	0	7 (6)	7 (4)
Thrombocyte counts	0	0	0

Source : Source : Table 36 on Page 103 in dmd114044csrbody.pdf

The labeling proposes strategies to handle these safety findings. Please refer to the review by Dr Evelyn Mentari, Clinical Safety Reviewer, DNP, for further details.

Immunogenicity Findings

The total incidence of anti-drug antibodies (ADA) formation was 29.4% in 109 patients during 48-week drisapersen treatment. Trough concentrations of drisapersen were increased by 130% in patients who were ADA positive compared to those who were ADA negative on Week 47. Given the multiple confounding factors associated with the disease, the impact of ADA on 6MWD is inconclusive.

It seems that ADA unlikely has an impact on AEs/SAEs and relevant lab parameters based on the available data.

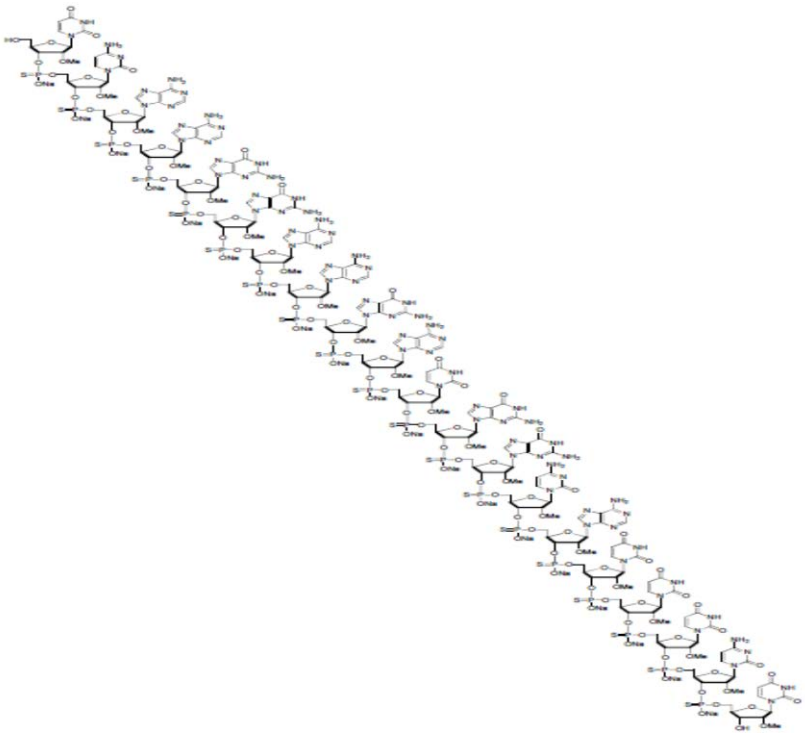
2 QUESTION BASED REVIEW

2.1 General Attributes of the Drug

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Drisapersen (GSK2402968 and PRO051) is a 20mer chemically-modified antisense oligonucleotide with molecular mass of 7395.27 (averaged isotopic distribution).

Drisapersen sodium solution, 200 mg/mL is a sterile, clear, colorless to yellow solution, essentially free from particulates, containing 200 mg/mL of drisapersen sodium (the sodium salt of a 20-mer 2'-O-methyl-phosphorothioate oligoribonucleotide). The structure of drisapersen sodium is presented below:



2.1.2 What are the proposed mechanism of action and therapeutic indications?

Drisapersen is an exon skipping oligonucleotide inducer of dystrophin synthesis indicated for the treatment of Duchenne muscular dystrophy (DMD) with mutations in the dystrophin gene that are amenable to treatment with exon 51 skipping as determined by genetic testing.

2.1.3 Should drisapersen be indicated for patients amenable to exon-51 skipping who were not studied in the clinical development program?

Yes. Despite studying nine different DMD mutations amenable to exon-51 skipping, not all amenable mutations were enrolled in the clinical development program. Proposed product labeling states that drisapersen is to be indicated for all DMD mutations that are amenable to treatment with exon 51 skipping. In theory, drisapersen can restore the mRNA reading frame to produce an internally-deleted dystrophin for a number of DMD deletion mutations not studied in the clinical development program.

Patients with other ultra-rare DMD deletion mutations that are amenable to exon-51 skipping do exist (e.g. 13-50, 52-63). For some amenable mutations only 1-2 patients exist in the DMD Leiden database (www.dmd.nl). Given the strict inclusion criteria for the drisapersen clinical trials, these patients may have been ineligible to participate. Hence, given the lack of available subjects for study, coupled with inherent heterogeneity in disease, along with the unknowns regarding the functionality of the internally-deleted dystrophin; determining efficacy in patients with ultra-rare DMD mutations amenable to exon-51 skipping is difficult. Last, there are no reasons to believe that the safety of drisapersen is in any way different in these ultra-rare populations of patients. Thus, if drisapersen is ultimately found to be safe and effective to warrant approval, then drisapersen should be indicated for all exon-51 amenable mutations.

2.1.4 What are the proposed dosages and routes of administration?

The proposed dosage and route of administration is the following:

- Loading dose: Initiate with 6 mg/kg twice weekly for the first 3 weeks of treatment
- Maintenance dose: 6 mg/kg once weekly
- Administer drisapersen subcutaneously. Rotate injection sites

Patients should receive concomitant glucocorticosteroid therapy during drisapersen treatment. The dosing regimen was evaluated in Study DMD 114117 (A phase II, double blind, exploratory, parallel-group, placebo-controlled clinical study to assess two dosing regimens of GSK2402968 for efficacy, safety, tolerability and pharmacokinetics in ambulant subjects with Duchenne muscular dystrophy).

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and the clinical studies used to support dosing or claims?

The dosing and claims are based on changes in 6 minute walk distance (primary endpoint) in double blind, randomized, placebo controlled studies. Studies DMD114117, DMD114678 are 48 weeks in duration with the primary endpoint at 24 weeks. The Phase III clinical trial design is similar to early clinical studies with the primary endpoint at 48 weeks. There were differences in entry criteria between early clinical studies and Phase

III study. Early clinical studies enrolled patients who could rise from the floor within 15 seconds. In Phase III study, this enrollment criteria was not implemented. Patients with rise time greater than 15 seconds have worse prognosis.

2.2.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

The response endpoint in clinical trials is 6 minute walk distance. This endpoint is not measured in clinical pharmacology studies.

2.2.3 Are the active moieties in plasma appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes.

2.2.4 Exposure-Response

2.2.4.1 What are the characteristics of the exposure-response relationships for efficacy?

A link between drisapersen plasma or muscle biopsy concentrations with changes in 6MWD cannot be definitively quantified at this time. The drisapersen treated group (6 mg/kg) relative to placebo in study DMD114117 and DMD114876 showed improvement in 6MWD; these studies (combined) had 36 patients receiving drisapersen. In study DMD114044, 122 patients were treated with 6 mg/kg drisapersen. In this study, drisapersen did not show any benefit relative to placebo.

The reviewer conducted analyses to understand differences in findings across studies. Drisapersen plasma concentrations collected pre-dose were compared across studies (Table 2). Table 2 shows that at Week 24 drisapersen pre-dose plasma concentrations were similar across the studies. Hence, differences in efficacy between studies are due to factors other than drisapersen concentrations.

Table 2. Drisapersen Plasma Concentration at Pre-dose in Studies DMD114044, DMD114876, DMD114117.

Visit	n	Trough concentration (ng/mL) Median (SD)
Week 8	47	12.7 (747)
Week 12	47	19.1 (12.9)
Week 24	49	40.9 (37.3)
Week 36[a]	38	55.2 (1059)
Week 48	106	61.4 (576)

Study DMD114044

Source: Table 60 on Page 132 in dmd114044csrbody.pdf. Shown are median (SD)

Parameter	Week 0		Week 12		Week 23	
	n		n		n	
C168 (ng/mL)[1]	5	5.1 (118)	7	21.1 (76.4)	7	35.8 (92)

Study DMD114876

Source: Table 64 on Page 149 in dmd114876csrbodyefficacy.pdf. Shown are geometric mean (%CV)

Visit	6 mg/kg Drisapersen Continuous	
	n	Concentration (ng/mL) [a]
Week 1 Day 1	18	0.00
Week 1 Day 4	18	5.86 ± 10.3
Week 24	16	27.1 ± 19.1
Week 29	18	37.9 ± 27.8
Week 34	17	37.4 ± 40.7
Week 37	17	47.9 ± 84.2

Study DMD114117

Source: Table 58 on Page 128 in dmd114117csrbody.pdf. Shown are median (SD)

While not definitive, the failure of DMD114044 could be due to enrollment of patients with advanced stage of the disease. To identify reasons the reviewer characterized disease progression and looked at influence of baseline prognostic factors such as age, 6MWD, rise time, corticosteroid dosing regimen on the rate of change in 6MWD. The analysis showed that age, 6MWD and rise time influence the rate of change in 6MWD. These findings are similar to those reported in literature for other mutations. It is the opinion of the reviewer that more research is needed to identify other potential prognostic factors such as physiotherapy and concomitant medications for cardiac related issues on the rate of change in 6MWD and ultimately their inclusion in exposure response analyses.

2.2.4.2 What are the characteristics of the exposure-response relationships for safety?

The adverse events (AEs) of interest are injection site reactions, thrombocytopenia and glomerular nephritis. Table 3 shows the adverse events of special interest by time to first occurrence in study DMD114876. The onset of injection site reactions in treatment group is less than a week in some patients. Analysis linking drisaperen concentrations with safety was not conducted.

Table 3. AEs of Special Interest by Time to First Occurrence (Safety Population) in Study DMD114876

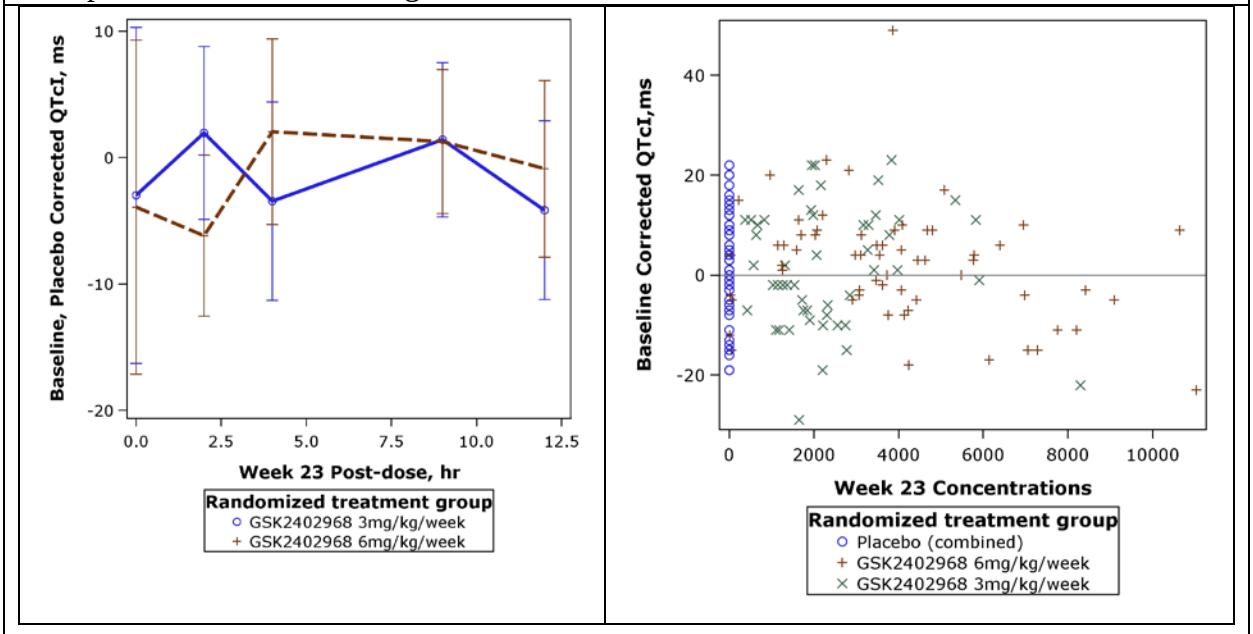
Treatment Group/ Special Interest Category	Number (%) of Subjects Time Since Start of Study Medication											
	<1 Week	<2 Weeks	<3 Weeks	<4 Weeks	<8 Weeks	<12 Weeks	<16 Weeks	<20 Weeks	<24 Weeks	<36 Weeks	<48 Weeks	≥48 Weeks
Placebo (N=16)												
Any AE of Special Interest	0	0	0	0	0	3 (19)	6 (38))	8 (50)	9 (56)	9 (56)	9 (56)	0
Injection site reaction	0	0	0	0	0	2 (13)	5 (31)	5 (31)	5 (31)	6 (38)	6 (38)	0
Renal effects	0	0	0	0	0	1 (6)	1 (6)	4 (25)	5 (31)	5 (31)	5 (31)	0
Inflammation	0	0	0	0	0	0	0	0	1 (6)	1 (6)	1 (6)	0
Coagulation	0	0	0	0	0	0	1 (6)	1 (6)	1 (6)	1 (6)	1 (6)	0
Hepatic effects	0	0	0	0	0	0	0	1 (6)	1 (6)	1 (6)	1 (6)	0
Thrombocyte counts	0	0	0	0	0	0	0	0	0	0	0	0
Drisapersen 3 mg/kg (N=17)												
Any AE of Special Interest	4 (24)	8 (47)	9 (53)	9 (53)	10 (59)	10 (59)	11 (65)	11 (65)	11 (65)	11 (65)	11 (65)	0
Injection site reaction	3 (18)	8 (47)	9 (53)	9 (53)	10 (59)	10 (59)	11 (65)	11 (65)	11 (65)	11 (65)	11 (65)	0
Renal effects	1 (6)	1 (6)	1 (6)	1 (6)	2 (12)	2 (12)	2 (12)	2 (12)	2 (12)	2 (12)	2 (12)	0
Inflammation	0	0	0	1 (6)	1 (6)	1 (6)	1 (6)	1 (6)	1 (6)	1 (6)	1 (6)	0
Coagulation	0	0	0	0	0	0	0	0	0	0	0	0
Hepatic effects	0	0	0	0	0	0	0	0	0	0	0	0
Thrombocyte counts	0	0	0	0	0	0	0	0	0	0	0	0
Drisapersen 6 mg/kg (N=18)												
Any AE of Special Interest	6 (33)	9 (50)	9 (50)	10 (56)	13 (72)	15 (83)	16 (89)	16 (89)	16 (89)	16 (89)	16 (89)	0
Injection site reaction	6 (33)	8 (44)	8 (44)	9 (50)	11 (61)	13 (72)	13 (72)	13 (72)	13 (72)	13 (72)	13 (72)	0
Renal effects	0	0	0	0	2 (11)	4 (22)	4 (22)	4 (22)	5 (28)	5 (28)	5 (28)	0
Inflammation	1 (6)	2 (11)	2 (11)	3 (17)	3 (17)	3 (17)	3 (17)	3 (17)	5 (28)	5 (28)	5 (28)	0
Coagulation abnormalities	0	0	0	0	0	0	1 (6)	1 (6)	1 (6)	1 (6)	1 (6)	0
Hepatic effects	0	0	0	0	0	0	1 (6)	1 (6)	1 (6)	1 (6)	1 (6)	0
Thrombocyte counts	0	0	0	0	0	0	0	0	0	0	0	0

Source : Table 38 on Page 109 in dmd114876csrbodyefficacy.pdf

2.2.4.3 Does this drug prolong QT/QTc Interval?

No formal TQT study was conducted although the sponsor collected information on QT in various studies. No large changes in mean QT interval were detected in an efficacy study (DMD114876). In this clinical study, patients were randomized to placebo, 3 mg/kg and 6 mg/kg drisapersen administered weekly. Each group consisted of 16-18 patients. The largest upper bound of the 2-sided 90% confidence interval (CI) for the mean change from baseline (placebo corrected) was less than 10 ms after administration of drisapersen on Week 23 (Figure 3). Evidence of dose response on QT prolongation was not observed. Baseline corrected QTcI did not show any relationship with drisapersen concentrations (Figure 3).

Figure 3: (Left) Mean and 90% CI ΔΔQTcI Time Course for Drisapersen Treatment Groups. (Right) Relationship Between Baseline Subtracted QTcI,msec and Drisapersen Concentrations, ng/mL



2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known E-R relationship?

Preclinical and clinical findings, according to sponsor, led 6 mg/kg to be considered the maximum tolerated dose.

PK modeling suggested that with a loading dose regimen of twice weekly dosing for 3 weeks, on average approximately steady state drisapersen concentrations are achieved 6 weeks earlier compared to weekly administration. Hence, all subjects in the successful study DMD114117 received a twice-weekly loading dose of 6 mg/kg (or placebo) for the first 3 weeks to achieve plasma levels of drisapersen that are anticipated to provide a therapeutic response, thereby potentially providing a faster clinical benefit. However, patients in the Phase III study DMD114044 did not receive loading doses.

The dose selection for DMD114044 was based on open-label clinical study with drisapersen in subjects with DMD. PRO051-02 (DMD114673 [acute phase]), showed exon 51 skipping with doses of 2 to 6 mg/kg given weekly for 5 weeks. No differences were observed with regard to muscle function and muscle strength between dose groups, or change over time within any dose group. However, it was likely that the duration of dosing was too short to demonstrate any functional changes. Subjects then received drisapersen 6 mg/kg/week for at least 48 weeks in the open-label extension to PRO051-02 (DMD114673 [extension phase]), and it was generally well tolerated. The efficacy data obtained at the 24-week timepoint in the open-label extension for study PRO051-02 (DMD114673 [extension phase]) suggested that the 6 mg/kg/week dose provided a clinically meaningful benefit in the majority of subjects, with a mean change in the 6MWD test of 36.8 m (range -58 m to +115 m) and was therefore supportive of the choice of dose in for study DMD114044.

Dose selection for DMD 114876 was based on PK/PD modeling. Based on PK/PD modeling, it was predicted that at steady-state, the 6 mg/kg/week dose would induce dystrophin expression greater than 30% of control. The 3 mg/kg/week dose was chosen as modeling predicted 3 mg/kg/week of drisapersen would produce dystrophin expression in the range of 18-22%.

There is lack of reliable data on dystrophin expression in DMD114044 to confirm model based predictions.

2.2.4.5 Immunogenicity

2.2.4.5.1 What is the incidence (rate) of the formation of the anti-product antibodies (APA), including the rate of pre-existing antibodies, the rate of APA formation during and after the treatment, time profiles and adequacy of the sampling schedule?

Sparse PK plasma samples in clinical study DMD114044 were analyzed for anti-drug antibody (ADA). A summary of ADA detected in all evaluable plasma samples of patients in the study is presented in the table below:

Study Week	Number of positive subjects and titer information	Placebo Subjects	Treated Subjects
0	Positive /total (total of samples analysed)	1/17 (47)	0/0 (0)
	Median titer (range)	200 (200)	NA
	Rate of ADA formation (%)	5.9	NA
8	Positive /total (total of samples analysed)	0/23 (23)	1/47 (47)
	Median titer (range)	NA	50 (50)
	Rate of ADA formation (%)	NA	2.1
12	Positive /total (total of samples analysed)	0/25 (25)	0/46 (46)
	Median titer (range)	NA	NA
	Rate of ADA formation	NA	NA

24	Positive /total (total of samples analysed) Median titer (range) Rate of ADA formation (%)	0/13 (13) NA NA	8/51 (51) 300 (100-3200) 15.7
36	Positive /total (total of samples analysed) Median titer (range) Rate of ADA formation (%)	0/17 (17) NA NA	10/41 (41) 1000 (50-6400) 24.4
47/48	Positive /total (total of samples analysed) Median titer (range) Rate of ADA formation (%)	0/50 (50) NA NA	30/107 (107) 800 (100-6400) 28.0
Total positive subjects (%)		1 /50 (2)	32/109 (29.4)

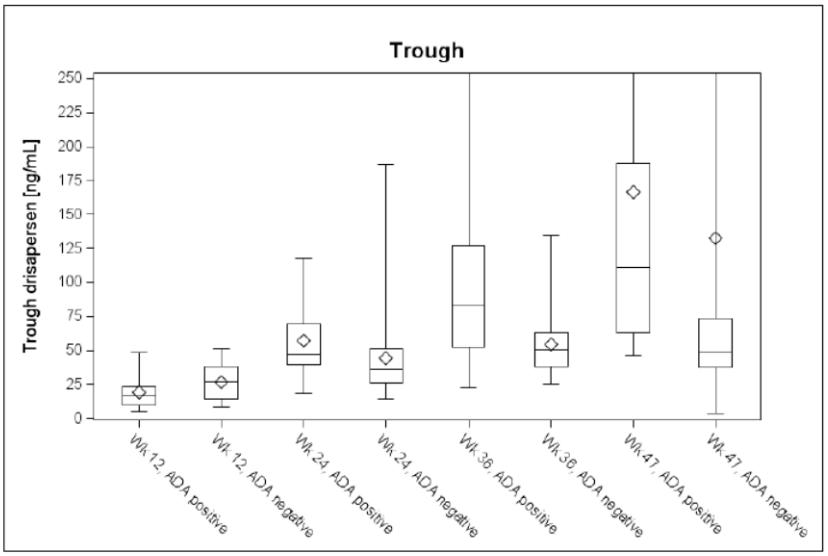
ADA formation is mainly detected after 12 weeks of drug treatment, at Weeks 24, 36, and 47/48. The incidence of ADA formation is 15.7% on Week 24, 24.4% on Week 36, and 28% on Week 47/48. The total incidence of ADA formation is 29.4% in 109 patients during the drug treatment.

One patient in placebo group showed ADA formation at Week 0.

2.2.4.5.2 Does the immunogenicity affect the PK of the therapeutic protein?

Yes. Trough concentrations of drisapersen are increased in ADA positive patients compared to those of ADA negative, which is more pronounced on Weeks 36 and 47. For instance, median trough concentrations of drisapersen are increased by 130% in ADA positive patients to those of ADA negative patients at Week 47.

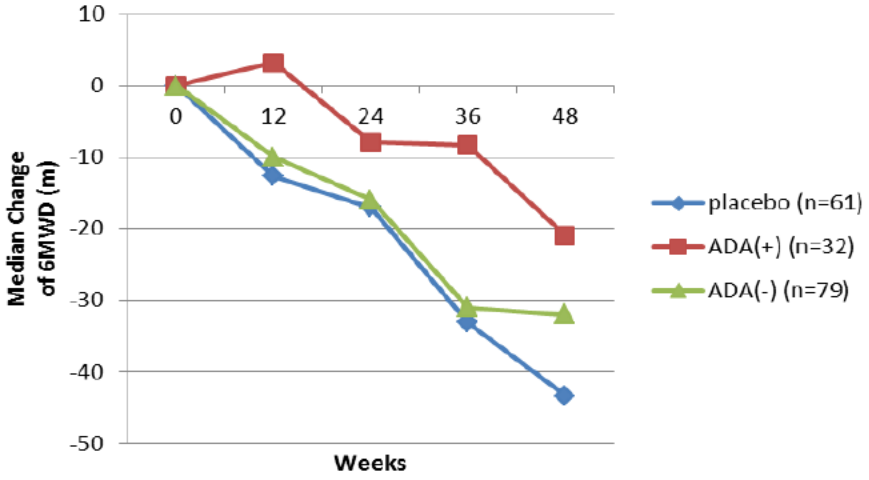
Figure 2.1: Boxplot of Drisapersen Trough Concentrations by Visit



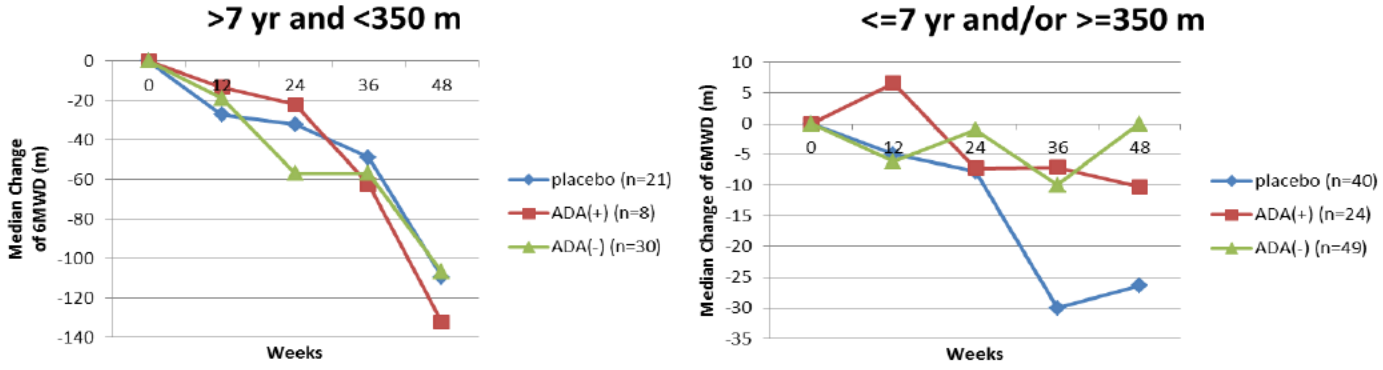
2.2.4.5.1 What is the impact of anti-product antibodies on clinical efficacy?

Due to multiple confounding factors associated with the disease, the impact of ADA on 6MWD is inconclusive based on the available data.

ADA positive patients showed a consistent less pronounced decline in mean and median change from original baseline in 6MWD at all visits compared to ADA negative subjects (Figure showed below).



However, unbalanced baseline age and the associated baseline 6MWD can contribute to the difference on 6MWD between ADA positive and negative patients (figure shown below).



2.2.4.5.2 What is the impact of anti-product antibodies on clinical safety?

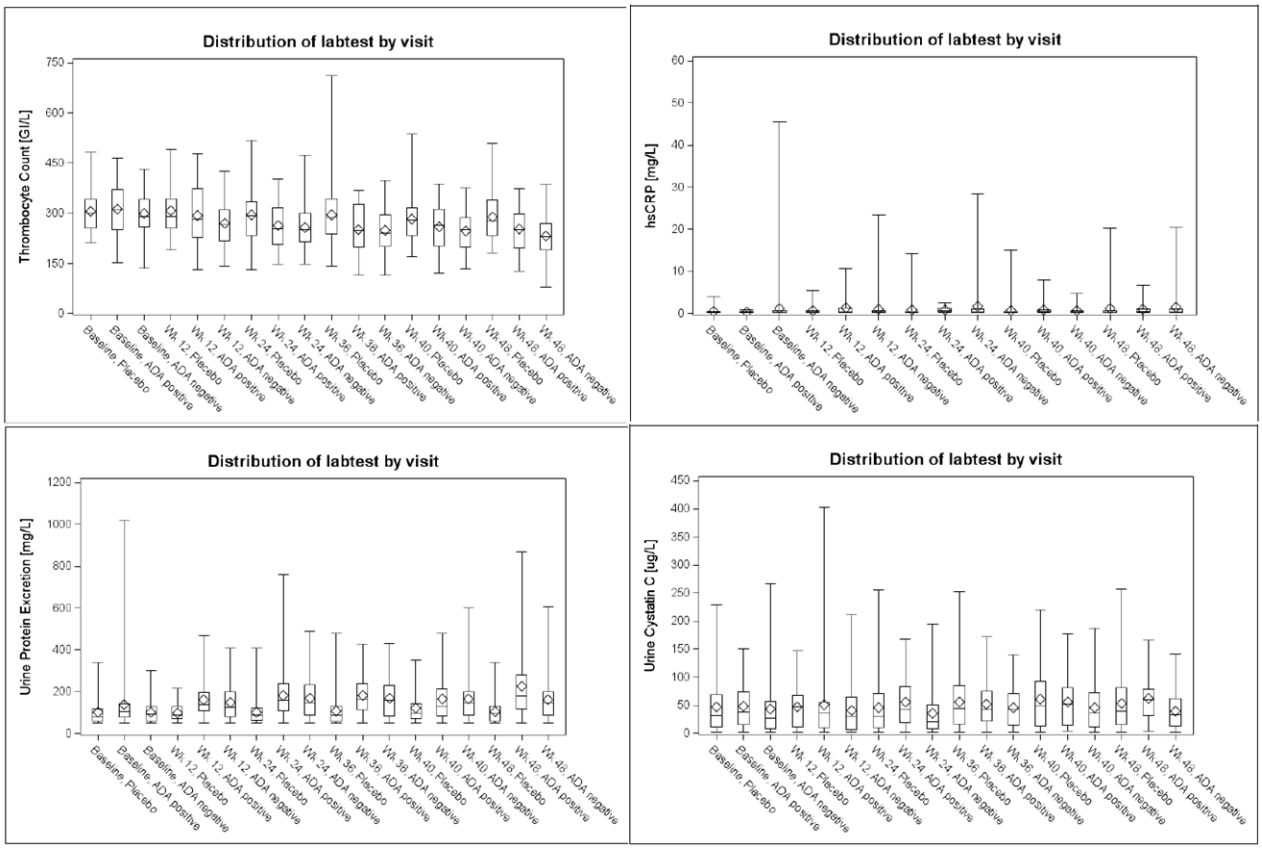
It seems that ADA unlikely has an impact on AEs/SAEs and relevant lab parameters based on the available data.

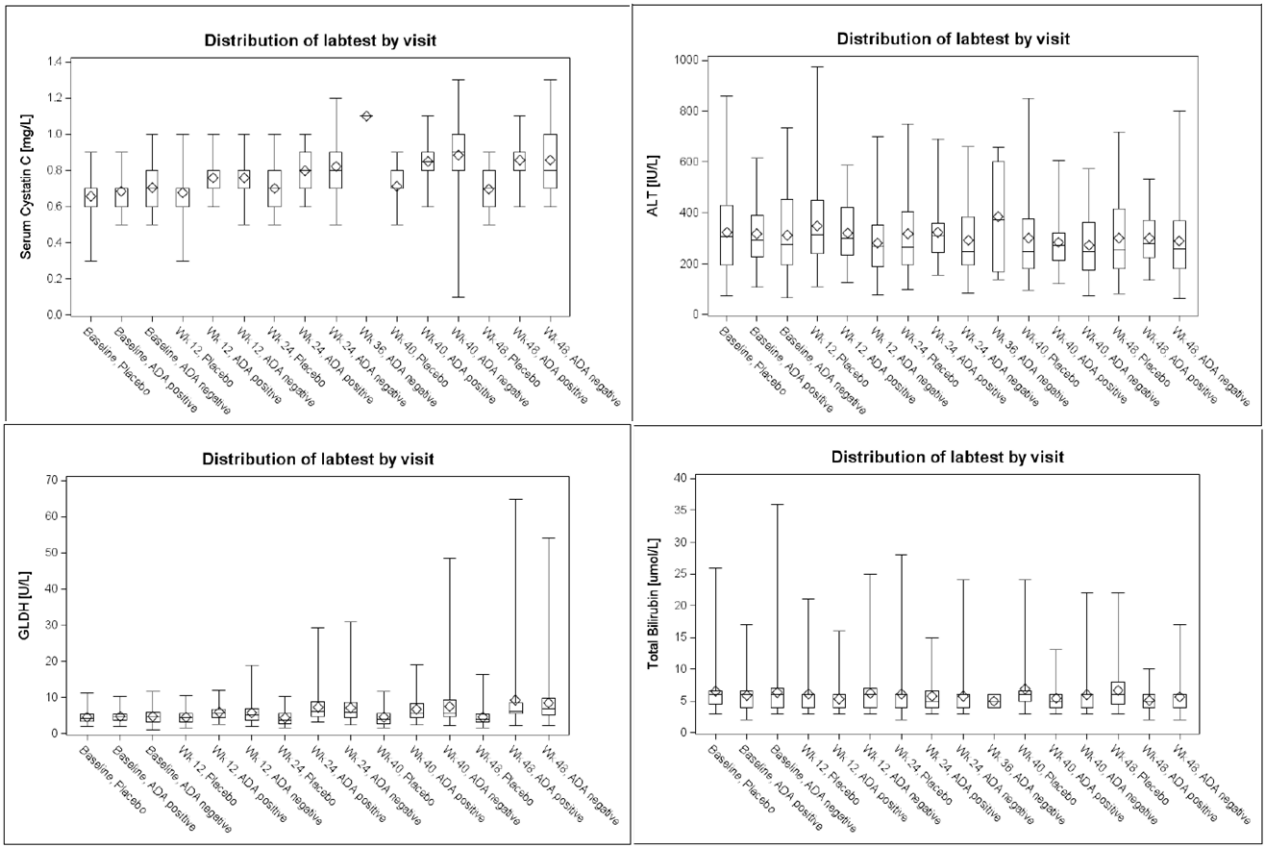
The first ADA positive sample for all except one ADA positive subject was at Week 24 or later. Therefore, only (S)AEs starting from Week 24 onwards were included in the analysis. None of the SAEs included in the analysis were drug related. Three SAEs (Subject 527, Glomerulonephritis, Subject 1270 Intracranial venous sinus thrombosis and

spinal pain) excluded from the analysis were drug related. All three SAEs occurred after Week 24 in subjects with inconclusive ADA status. Subjects on active treatment who have only negative ADA samples, but did not have an end of study sample were considered inconclusive regarding ADA status and were excluded from the analysis.

No increase in the percentage AEs, AESIs (injection site reaction, renal toxicity, inflammation, hepatic toxicity, coagulation, thrombocytes) was observed in ADA positive subjects, compared to ADA negative subjects. There is an over 1 fold increase of SAE in ADA positive patients compared to negative patients: One SAE (myocardial ischaemia), 3% of patients in ADA positive group; two SAEs (lumbar vertebral fracture and tibia fracture), 1% of patients in ADA negative group.

All laboratory parameters were generally in the same range with similar mean/median between ADA positive and ADA negative patients for all visits (figures showed below).





2.2.4.5.3 What is the incidence (rate) of the formation of the anti-dystrophin antibodies?

There is no reliable data on the incidence of the formation of anti-dystrophin antibodies.

Since dystrophin protein is theoretically lacking in DMD patients and a truncated-form of the protein produced by drisapersen treatment could elicit an immune response, serum samples had been collected from patients in clinical studies except for PRO051-01 to test the presence of anti-dystrophin antibodies using western blot analysis. A summary of results of the detection of anti-dystrophin antibodies in the clinical studies is presented below:

Study	Total number subjects evaluated	Anti-dystrophin antibody in placebo treated subjects		Anti-dystrophin antibody in drisapersen treated subjects	
		Subjects evaluated (n)	Positive subjects in any sample (n (%))	Subjects evaluated (n)	Positive subjects in any sample (n (%))
DMD114673 (acute phase)	12	na	na	12	0
DMD114673 (extension phase)	12	na	na	12	0
DMD114117	53	18	0	35	0
DMD114118	20	5	0	15	0
DMD114876	51	16	0	35	0
DMD114044	186	61	2 (3%)	125	1 (1%)
DMD114349	233	na	na	233	9 treated / 5 placebo(5%)
Total	**567**	**100**	**2 (2%)**	**467**	**12 (3%)**

Note: Note: All studies described in this section were performed using the sodium salt of drisapersen. Drisapersen sodium may be referred to as drisapersen, PRO051, GSK2402968, or h51AON23 in the study reports provided.
Key: n: number of subjects, na: not applicable, since the DMD114673 and the DMD114349 studies were open-label studies

The data showed that the rate of the formation of anti-dystrophin antibodies is low (3%) in drisapersen treated patients, which is comparable with that of placebo patients (2%).

A limitation of the assay is that the western blotting was performed using full-length dystrophin protein. In the unlikely event that an induced anti-dystrophin antibody would be only specific to the epitope unique to the truncated form of the protein resulting from the exon-skipping treatment, this antibody may not be detected with this assay. In addition, no confirmatory assay could be developed as no purified dystrophin protein is available so any positive samples could not be confirmed. Thus, the incidence of the formation of anti-dystrophin antibodies is inconclusive.

2.2.5 What are the PK characteristics of the drug?

2.2.5.1 What are the single and multiple dose PK parameters?

The current submission consisted of 7 clinical studies to characterize single and multiple dose-PK of drisapersen for DMD patients between doses of 0.5 mg/kg/week and 9 mg/kg/week (for 9 mg/kg dose level, only single dose PK was evaluated).

A summary of main PK parameters (Cmax and AUC0-24h) and tissue levels of drisapersen in the clinical studies is shown below:

Study Ref No	Treatments (route, dose, regimen)	Parameter				Mean tissue concentration [c]		Study summary location
		Cmax (µg/mL) [a]		$AUC_{0\text{-}24h}$ (µg.hr/mL) [b]		(µg/g)	wk in study	
		Day 1	End of study	Day 1	End of study			
DMD114673 (acute phase)	SC, 0.5 mg/kg/wk for 5 weeks SC, 2 mg/kg/wk for 5 weeks SC, 4 mg/kg/wk for 5 weeks SC, 6 mg/kg/wk for 5 weeks	1.69 3.62 5.27 9.13	1.02 4.11 6.80 11.0	7.5 26.9 40.8 76.7	5.9 25.9 44.2 103	- - - 6.9	- - - 5	section 2.2.1.2.1
DMD114673[d] (extension phase)	SC, 6 mg/kg/wk SC, start of re-dosing	- 8.2	8.7 -	- 105	103 -	14.4 20.3	24 69	section 2.2.3.1.1
DMD114118	SC, 3 mg/kg single dose SC, 6 mg/kg single dose SC, 9 mg/kg single dose	4.99 8.14 8.94	- - -	44.6 87.8 97.8	- - -	- - -	- - -	section 2.2.2.1.1
DMD114117[e]	Continuous: SC, 6 mg/kg/wk or Intermittent: alternating 6 mg/kg biweekly and 6 mg/kg/wk for 6 weeks followed by 4 weeks off-dose period	- -	4.85 4.81	- -	45.5 52.5	11.0 9.8	24 24	section 2.2.2.2.1
DMD114876[f]	SC, 3 mg/kg for 24 weeks SC, 6 mg/kg for 24 weeks	3.05 5.73	2.84 6.24	23.0 46.7	30.2 57.3	2.7 10.8	24 24	section 2.2.2.3.1
DMD114044	SC, 6 mg/kg/wk for 48 weeks	-	-	-	-	4.1 5.2 9.3 16.6 14.0	8 12 24 36 48	section 2.2.2.4.1
DMD114349[g]	SC, 6 mg/kg/week up to 104 weeks divided into sub-groups of placebo in feeder study active treatment in feeder study	 5.68 5.81	 6.57 6.22	 55.2 58.4	 80.3 74.1			section 2.2.3.2.1

Note: All studies described in this section were performed using the sodium salt of drisapersen. Drisapersen sodium may be referred to as drisapersen, PRO051, GSK2402968, or h51AON23 in the study reports provided. PK parameters are reported in ng in the reports, however stated in µg in this summary document

Key:

a Geometric mean (CV%) ; b Median (range); c mean tissue concentrations provided in µg/g tissue; wk is the week in which the biopsy was obtained during the study; d up to 177 weeks; tissue concentrations reported are from visit 37 (week 24) and visit 81 (week 69) respectively, re-dosing commenced approximately one year after week 177; e no profile obtained at first dose, end of study is 29 week; subjects started with SC 6 mg/kg twice weekly for 3 weeks and thereafter continued with either the continuous or intermittent regimen; tissue concentrations determined in tibialis anterior muscle reported here (quadriceps excluded from mean); f tissue concentrations at week 24 reported in table; g Cmax and AUC reported are from subjects who had PK profiles on both occasions, end of study is week 48 profile, subjects were dosed up to 104 weeks

- = not determined/available; SC.=subcutaneous, wk = week

Following single dose administration, the inter-subject variability (% CV) at lower dose levels at 0.5 – 2 mg/kg was 66-75% for Cmax and 14-30% for AUC0-t. This large inter-subjects variability for Cmax was decreased to 20-50% following 5 weekly doses.

Overall, at dose levels of 3-9 mg/kg the inter-subject variability (% CV) was 7-48% for Cmax and 12-48% for AUC0-t following single dose administration. Following multiple doses of 3-6 mg/kg/week, the inter-subject variability (% CV) was low to moderate (22-46% for Cmax and 25-47% for AUC0-t).

Following multiple doses at 0.5 -2 mg/kg/week for 5 weeks, no obvious drug accumulation was observed. However following multiple doses at 6 mg/kg/week, AUC0-168 increased about 2-fold over 48 weeks of weekly dosing of drisapersen. Drug accumulation in muscle was also observed following multiple doses of drisapersen. In one study (DMD114044), mean concentrations of drisapersen in muscle tissue homogenates increased with increasing time up to about 36 weeks of dosing at 6 mg/kg/week.

Plasma trough levels and muscle levels increased over time with once weekly dosing and approach steady state after 24 weeks. Muscle tissue concentrations of drisapersen can be detected at 12 weeks after cessation of dosing at 3-6 mg/kg/week.

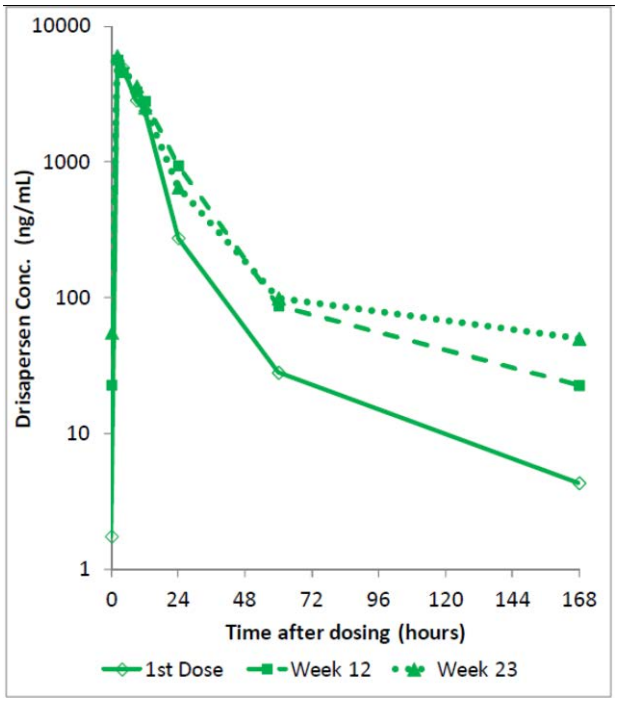
Extraction efficiency to determine drisapersen levels in muscle homogenates is unknown and the impact on accuracy has not been determined. Therefore the actual concentrations measured in tissue should be considered estimates.

2.2.5.2 How does the PK of the drug and its major metabolites in healthy adults compare to that in patients?

Drisapersen PK was evaluated in DMD patients.

2.2.5.3 What are the characteristics of drug absorption, distribution, metabolism and elimination)?

Following SC administration of drisapersen at 6 mg/kg/week, the median Tmax is between 2 and 4 hours. Mean drisapersen plasma concentration-time profiles following SC administration of 6 mg/kg/week after single and multiple doses are shown below:



Values of AUC0-24 of drisapersen are comparable following a 4-h IV infusion and a SC administration at 6 mg/kg.

Drisapersen is highly bound to human plasma protein in vitro (≥ 98.2%) at concentrations of 0.7 – 700 ug/mL.

Unchanged (parent) drisapersen was the major circulating drug-related component detected in the plasma. Minor metabolites resulting from the sequential loss of nucleotides from the 3' end were detected. Drisapersen is not expected to be a substrate of CYP450, and it's not an inhibitor or inducer of major CYP450 isozymes at the therapeutic dose in vitro.

Drisapersen and its shortened metabolites are excreted primarily in urine.

2.2.5.4 Based on PK parameters, what is the degree of linearity in the dose-concentration relationship?

Following single dose of drisapersen, over the dose range of 0.5 mg/kg to 6 mg/kg, Cmax and AUC parameters increased dose proportionally; however, less than dose proportionality has been shown between 6 mg/kg and 9 mg/kg.

Following multiple doses of drisapersen, there is a trend of dose proportionality between 3 mg/kg/week and 6 mg/kg/week.

2.2.5.5 How do the PK parameters change with time following chronic dosing?

Drispersen accumulation following weekly doses of 6 mg/kg has been observed in plasma and muscle tissues. Plasma trough levels and muscle levels increase over time with once weekly dosing and approach steady state after 24 weeks. Refer to Section 2.2.5.1.

2.2.5.6 What is the inter- and intra-subject variability of PK parameters in volunteers and patients?

Inter-individual variability on clearance is 20.3% and central volume of distribution is 20.3% and 26.6% respectively. The inter-occasion variability on absorption rate constant is 52.7%.

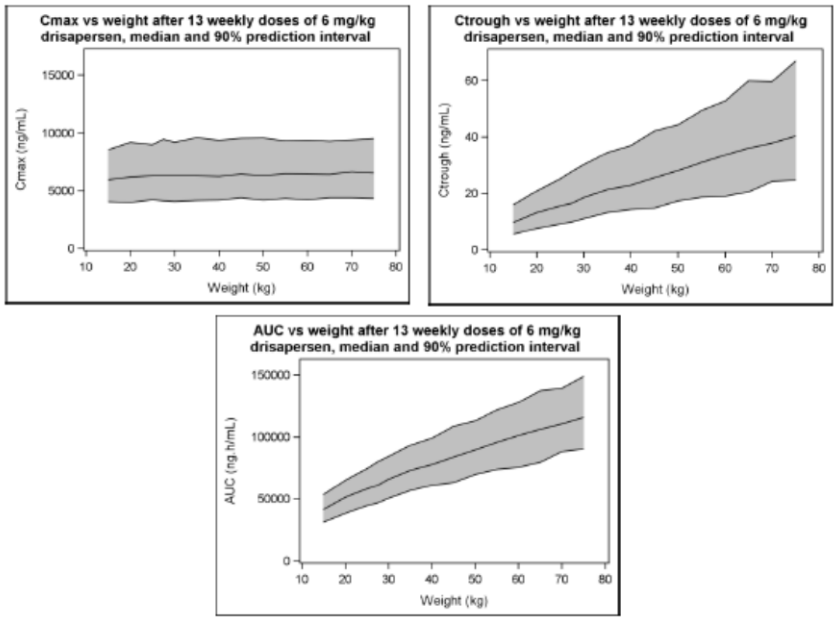
2.3 Intrinsic Factors

2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Factors influencing exposure

Body weight has an effect on exposure. Patients with higher body weight have higher AUC compared to lighter patients (Figure 4). There is no influence of body weight on Cmax when drisapersen is dosed on a mg/kg basis.

Figure 4. Predicted Week 13 drisapersen PK parameter estimates based on the final model (median and 90% prediction interval) versus body weight, for 6 mg/kg dosing. Top left: peak concentrations; top right: trough concentrations (before week 13 intake); bottom: AUC0-168h.



Source : Figure 14 on Page 59 in kns14082clinicalstudyreportincludingappendices.pdf

Factors influencing response

Baseline prognostic factors such as 6 minute walk distance, rise time, and age have an impact on DMD disease progression. Rise time is reported to be an early predictor of milestone events like loss of ambulation.

The Phase III trial DMD114044 conducted in 186 (N=124 in drisapersen group; N=62 in placebo group) patients did not show any treatment related benefit on 6MWD. The study enrolled patients with a wide range of rise time. DMD114117 was conducted in patients with rise time ≤ 7 seconds and showed treatment related benefit on 6MWD. DMD114876 study was conducted in patients with rise time <15 seconds. It is possible that differences in patient population characteristics could have contributed to differences between studies. It is not clear if the loading doses administered in DMD114117 study contributed towards a positive finding. However, drisapersen concentrations at 24 weeks were similar between the failed Phase III study and positive early clinical study (Table 2).

2.3.2 Based upon what is known about E-R relationships and their variability, what dosage regimen adjustments are recommended for each group?

2.3.2.1 Elderly

There are no labeling statements regarding dose adjustment in elderly. The patient population that would be treated with drisapersen would be younger.

2.3.2.2 Pediatric Patients

No dose adjustments are recommended. The dose/dosing regimen, as studied in DMD 114117, is the recommended dose in pediatric patients.

2.3.2.3 Race

Not enough information to determine the race impact on PK and the clinical responses of drisapersen. No dose adjustments are recommended.

2.3.2.4 Renal Impairment

Although renal related adverse events are reported, no specific dose adjustments are being proposed. For renal related adverse events, the label recommends:

Glomerular Renal Effects: Monitor urine protein. Suspend [TRADENAME] when urine protein is > 1 gram per 24 hours. Discontinue [TRADENAME] if patient develops glomerulonephritis

2.3.2.5 Hepatic Impairment

No clinical studies have been conducted to evaluate the PK of drisapersen in hepatic impaired patients. Hepatic metabolic function is less relevant to drisapersen as the main route of metabolism is through exonucleases and non-hepatic specific cytochrome enzymes.

Thus, no dose adjustments are recommended.

2.3.3 What pregnancy and lactation use information is there in the label?

Pregnancy
Risk Summary
Drisapersen has not been studied in female patients. Reproduction studies in female animals have not been conducted. It is not known whether drisapersen can cause fetal harm when administered to pregnant women or if drisapersen affects the female

reproductive capacity. The pharmacologic mechanism of action of drisapersen is not expected to result in adverse developmental outcomes.

Lactation
Risk Summary
Drisapersen has not been studied in female patients. It is not known whether drisapersen is excreted in human milk. The effect of drisapersen on human milk production or on the breast fed child has not been studied.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Analysis looking at the influence of extrinsic factors such as physiotherapy, concomitant medications other than corticosteroids on response was not conducted. It should be noted that patients in placebo and treatment groups were on stable corticosteroid doses.

2.4.2 What are the drug-drug interactions?

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

No.

Drisapersen is not expected to be a substrate of CYP450 enzymes, as the main route of its metabolism is through exonucleases and non-hepatic specific cytochrome enzymes.

Two in vitro studies have been conducted to evaluate the effect of drisapersen to inhibit or induce the major CYP enzymes in human hepatocytes. The studies show that drisapersen is unlikely to inhibit CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4/5, and is unlikely to induce CYPs 1A2, 2B6 and 3A4/5 at the proposed therapeutic dose.

2.4.2.2 Is the drug an inhibitor and/or an inducer of PGP transport processes?

Drisapersen is unlikely to be an inhibitor/or inducer of membrane transporters.

No studies have been conducted to evaluate drisapersen's potential interaction (as a substrate, inhibitor, or inducer) with uptake and efflux membrane transporters.

AONs (including drisapersen) appear to be taken up into cells via endocytosis and not by uptake membrane transporters. In addition, ASOs have long tissue half-lives, up to several weeks. Clearance from tissues is very slow and typically involves metabolism by exo- and endonucleases (though this latter appears less important for drisapersen). This suggests no involvement of membrane transporters.

2.4.2.3 Does the label specify co-administration of another drug?

Yes. Patients will receive concomitant corticosteroid therapy.

2.4.2.4 What other co-medications are likely to be administered to the target population?

Corticosteroids, beta blockers, ACE inhibitors, medications to manage pain and other co-morbidities.

2.4.2.5 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

No

2.4.2.6 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?

No

2.4.2.7 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

No

2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

No.

2.5 General Biopharmaceutics

2.5.1 What is the relative bioavailability of the proposed to-be-marketed formulation to the immediate release formulation?

The commercial formulation has been used in all clinical studies including the pivotal study (except for studies of PRO051-01 and PRO051-02). Thus, no formal comparative bioavailability or bioequivalence studies were conducted.

2.6 Comparing DMD114673 study with natural history cohort

DMD114673 is an open label long term study that evaluated efficacy of 6mg/kg drisapersen. Sponsor concluded that drisapersen improved walking ability in some patients when compared to matched controls from a natural history study. Do these findings provide supporting evidence of efficacy?

Reviewer's Comments: While improvements in 6MWD in some DMD114673 study patients could be due to drisapersen, definitive treatment benefit upon long term administration of drisapersen cannot be adequately quantified with the available data.

Sponsor's Analyses

Data

The natural history cohort data was obtained through an observational single center study recording functional time tests, pulmonary function, age, weight, height and medication use collected as part of routine follow-up clinics from genetically confirmed and corticosteroid treated DMD subjects attending the Leuven Neuromuscular Reference Centre (NMRC) for clinical care and management.

In the DMD114673, all subjects were genetically confirmed with DMD and as having a mutation suitable for exon 51 skipping therapy and were all receiving continuous corticosteroid treatment. Only one drisapersen subject (Subject 207) had a short period of intermittent corticosteroid treatment during the observation period. Of the 12 subjects enrolled, five subjects were in functional decline and seven subjects were stable in their functional abilities as assessed by their treating physicians. Subjects were originally dosed for five weeks in groups of three at 0.5, 2.0, 4.0, and 6.0 mg/kg/week of drisapersen, with a subsequent 13 week follow-up period. Following this dose escalation phase, and after a break of 6 – 15 months, subjects entered an extension study where they were treated with drisapersen at 6.0 mg/kg/week for 72 weeks. A break in dosing was implemented for eight weeks, and dosing recommenced at Week 81 on an intermittent regimen (8 weeks of 6mg/kg/week, 4 weeks no dosing = 12 week cycle) until Week 188. In addition to the 6 minute walk distance (6MWD), the rise from floor (RFF) times and the boy's pulmonary function were reviewed.

Data Analysis

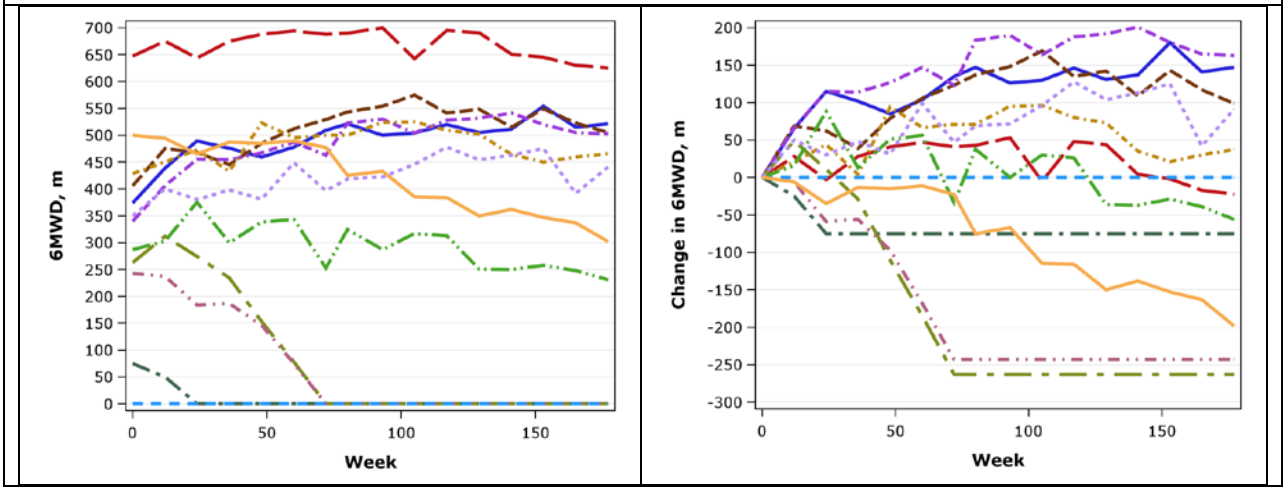
Two analyses were performed by matching according to DMD114673 baseline 6MWD and age, and baseline RFF and age. The matching criteria were pre-defined prior to any matching being performed and was based on recommendation from a N. Goemans and the McDonald publication showing the influence of age, baseline 6MWD, and other

timed function tests as reliable predictors of outcome (Pane, Mazzone et al. ; McDonald, Henricson et al. 2013; McDonald, Henricson et al. 2013).
Matching was performed by first identifying subjects within the natural history database that matched any of the 12 subjects from the DMD114673 study based on baseline age (within six months) and 6MWD (within 30 meters) or RFF (within 0.5 seconds). The first data-matched time point for the natural history cohort was used as the control baseline. The results from the 6MWD at this baseline time point were plotted together with the results for the applicable matched DMD114673 subject over time (with time being represented as age of the boys). All matches were plotted from the first matching record with the applicable DMD114673 subject at baseline onwards.

Results

Figure 5 shows the 6MWD data in 12 DMD114673 study subjects up to 168 weeks.

Figure 5. (Left) 6MWD (Right) Change from Baseline 6MWD in DMD 114673 Subjects. Data collected till 168 weeks is shown here.



A total of 75 natural history subjects matches with the 12 DMD114673 subjects were available and included in the analysis. Table 4 describes the number of natural history matches made based on age and 6MWD per DMD114673 subject and those excluded due to having no more than two assessments available. This table also presents the 6MWD range at baseline and the age range of the matched subjects over the assessment period to put into context the functionality expected from that particular group of DMD subjects. All matched natural history subjects are included in the per subject plots. Only matched natural history subjects with more than two assessments from the point of matching are including in the individual subject narratives.

Table 4. Number of natural history cohort matches per DMD114673 study subject

DMD114673 Subject	NH Matches Identified	NH Matches Included[a]	Subject Age Range (Years) during Observation Period		Baseline 6MWD Range (Metres)	
			DMD114673	Natural History	DMD114673	Natural History
101	5	2	10.9 – 14.3	10.5 - 14.1	374	356-399
102	10	7	8.0 – 11.4	7.6 – 12.4	406	377-435
103	1	0	11.8 – 15.2	11.7	75	60
104	0	0	10.3	N/A	647	N/A
105	10	4	9.2 – 12.6	8.8 – 13.9	340	315-366
106	3	1	9.6 – 13.0	9.4 – 13.0	263	275-281
107	6	4	11.4 – 14.8	11.1 – 15.6	243	221-248
201	13	0[b]	14.3 – 17.7	13.8 - 17.5	0	0
202	4	2	7.5 – 10.9	7.1 – 11.7	429	400-425
205	4	3	12.0 – 15.4	12.0 – 14.6	287	259-310
206	7	5	5.9 – 9.3	5.5 – 8.8	350	322-379
207	1	1	9.9 – 13.3	10.1 – 14.1	500	475

a. Subjects excluded if they did not have more than 2 assessments available - consideration was taken in terms of timeframe between those 2 assessments.
b. All subjects were non-ambulant and therefore full matching was not performed based on 6MWD

Source: Table 1 on Page 6 in dmd114673-nhclinicalstudyreportincludingappendices.pdf

Six of the drisapersen subjects ("101", "102", "105", "202", "206" and "207") were defined as having stable function at baseline (those with a 6MWD of at least 300 metres).

Figure 6, Figure 7, Figure 8 and Figure 9 show the change in 6MWD with age in individual subjects from the DMD114673 study. Also shown are changes in 6MWD for the matches from natural history.

Figure 6. Longitudinal Changes in 6MWD by Individual DMD 114673 Subjects (black solid line) Along With Natural History Matches Based on Age and Baseline 6MWD (solid color lines).

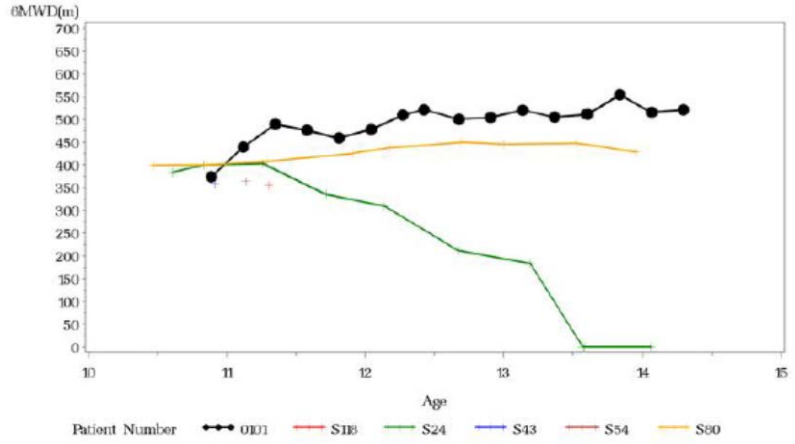
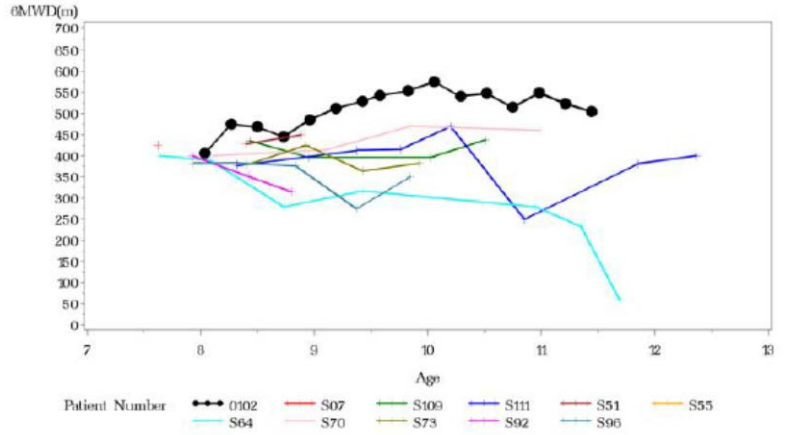
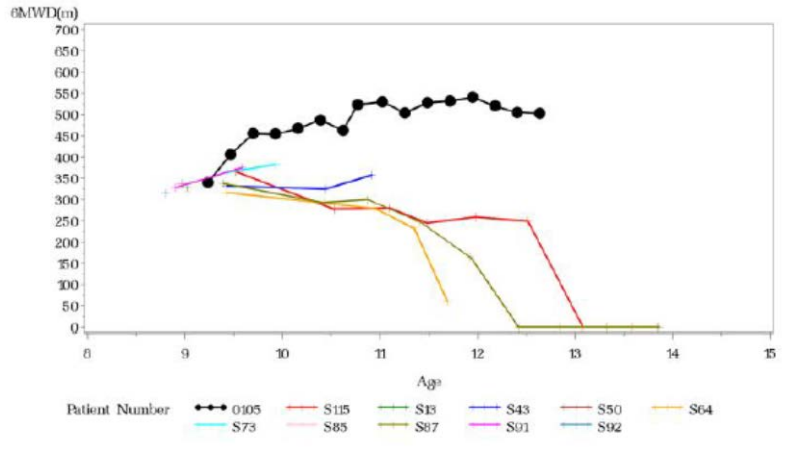
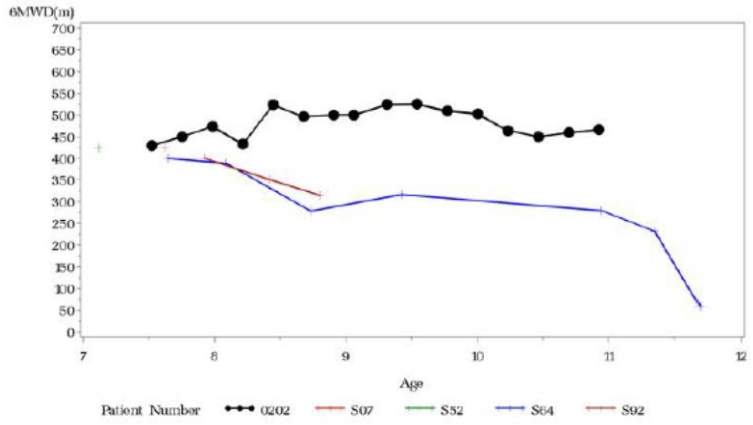
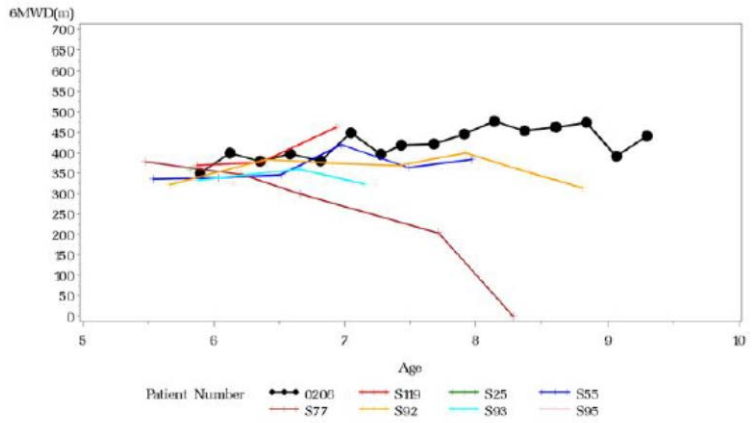
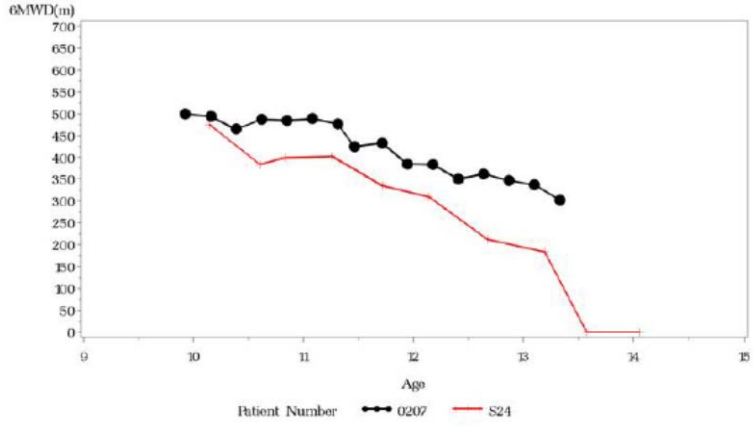
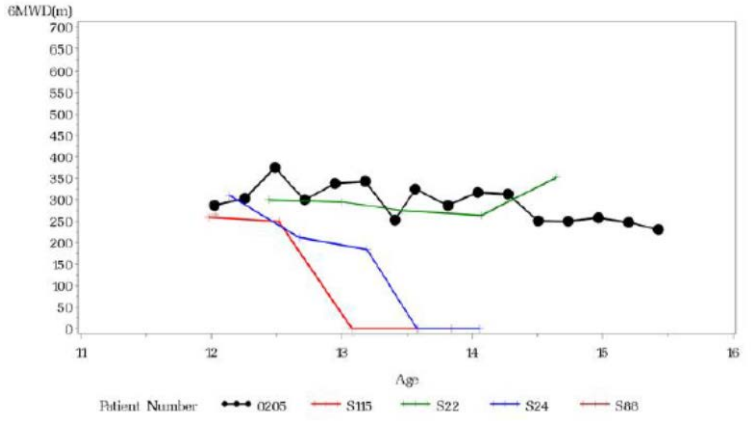
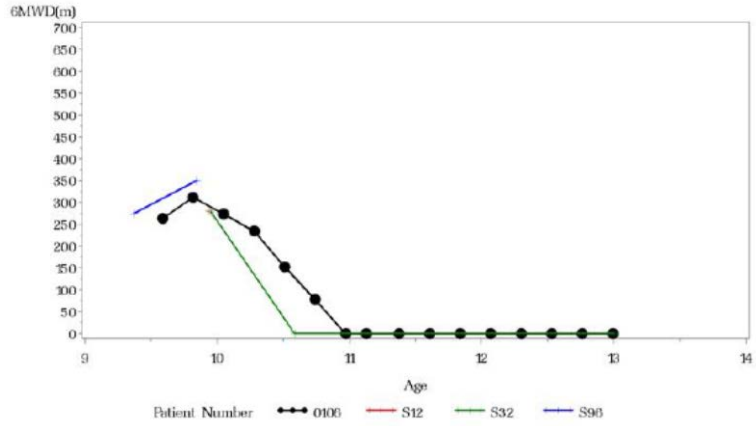
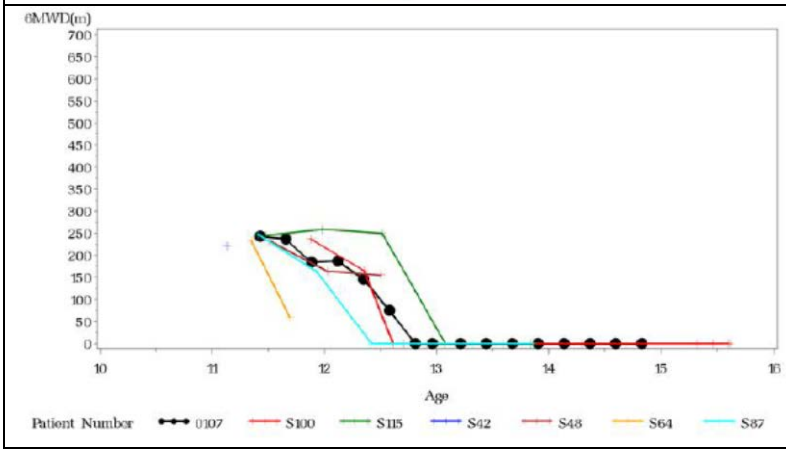
	Patient 0101 vs Natural History Matches • At 14 y, NH patient S80 walked 428 m (NH) while drisapersen treated patient walked 515 m. • Distance walked in 6 minutes improved by 87 m
	Patient 0102 vs Natural History Matches • At 11 y, NH patient S70 walked 461 m (NH) while drisapersen treated patient walked 549 m. • Distance walked in 6 minutes improved by 88 m.
	Patient 0105 vs Natural History Matches • At 11 y, NH patient S43 walked 358 m (NH) while drisapersen treated patient walked 530 m. • Distance walked in 6 minutes improved by 172 m.

Figure 7. Longitudinal Changes in 6MWD by Individual DMD 114673 Subjects (black solid line) Along With Natural History Matches Based on Age and Baseline 6MWD (solid color lines).

	Patient 0202 vs Natural History Matches • At 11 y, NH patient S64 walked 280 m (NH) while drisapersen treated patient walked 466 m. • Distance walked in 6 minutes improved by 186 m.
	Patient 0206 vs Natural History Matches • At 7 y, NH patient S119 walked 463m m (NH) while drisapersen treated patient walked 441 m at 9.3y. • Similar walking trajectory.
	Patient 0207 vs Natural History Matches • Decline in ambulation. Similar to NH match.

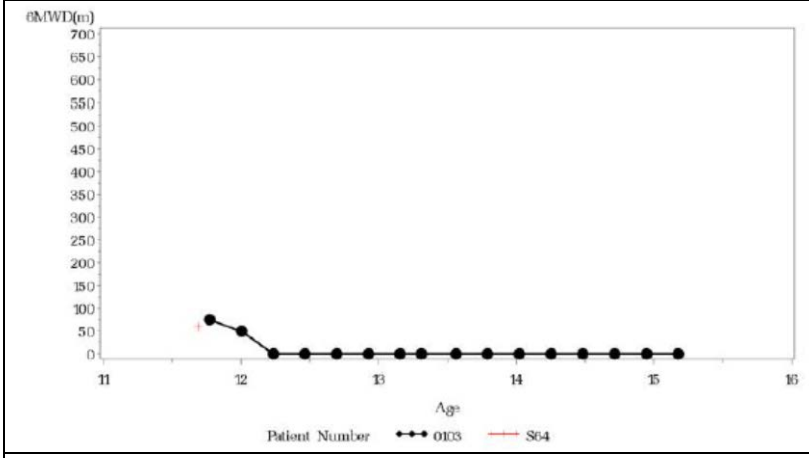
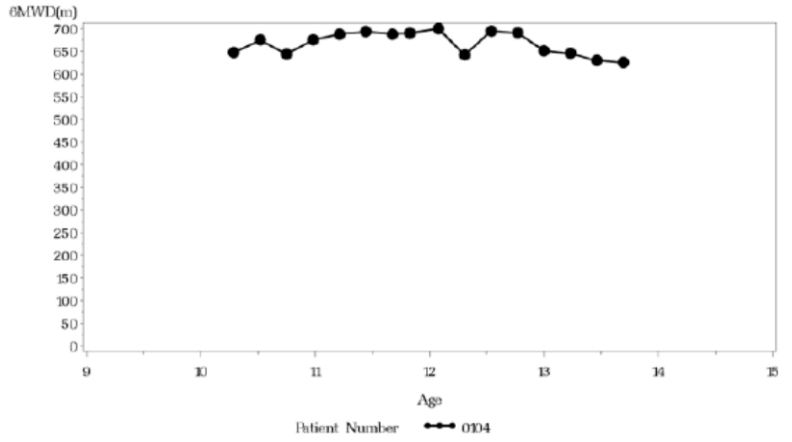
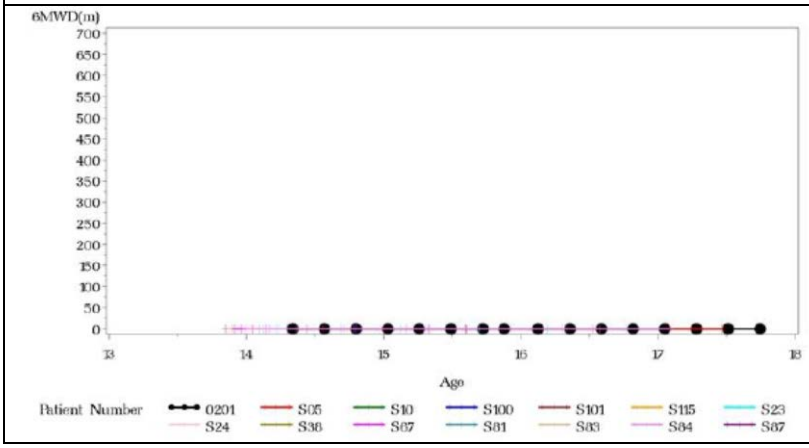
NA- Not Available

Figure 8. Longitudinal Changes in 6MWD by Individual DMD 114673 Subjects (black solid line) Along With Natural History Matches Based on Age and Baseline 6MWD (solid color lines).

	Patient 0205 vs Natural History Matches • Decline in ambulation. Similar to NH match.
	Patient 0106 vs Natural History Matches • Decline in ambulation. Similar to NH match.
	Patient 0107 vs Natural History Matches • Decline in ambulation. Similar to NH match.

NA- Not Available

Figure 9. Longitudinal Changes in 6MWD by Individual DMD 114673 Subjects (black solid line) Along With Natural History Matches Based on Age and Baseline 6MWD (solid color lines).

	Patient 0103 vs Natural History Matches • Decline in ambulation. No NH match.
	Patient 0104 vs Natural History Matches • Stable patient with baseline 6MWD of 650 m. No NH match.
	Patient 0201 vs Natural History Matches • Non ambulant patient at baseline. No NH match.

Sponsor's Conclusions

A matched control study has shown a clear difference in 6MWD when comparing subjects with stable baseline function treated with drisapersen over 3.4 years when compared with a natural history cohort (Table 5).

Table 5. Conclusions Based on Matching Analysis

Patient Number	Conclusions Based on Matching Analysis	Improvement in 6MWD compared to natural history
101	428 m (NH), 515 m (Drisapersen) at 14 y.	87 m
102	461 m (NH), 549 m (Drisapersen) at 11y.	88 m
103	No matches	
104	No matches. Baseline 6MWD > 600m.	
105	358 m (NH), 530 m (Drisapersen) at 11y.	172 m
106	Loss of ambulation. Similar match in NH.	
107	Loss of ambulation. Similar match in NH.	
201	Non ambulant.	
202	280 m (NH), 466 m(Drisapersen) at 11 y.	186 m
205	Decline in ambulation. Similar to NH match.	
206	463m (NH, 7y), 441 m(Drisapersen) at 9.3y. Similar trajectories.	
207	Decline in 6MWD. Similar to NH match.	

No drisapersen subjects with stable baseline function lost ambulation compared with 25% of natural history subjects. A difference was less evident in those with a declined baseline function, with the exception of one drisapersen subject who was still walking 231 meters unlike his DMD peers who had lost ambulation at the age of 15.4 years.

Reviewer's Analysis

The reviewer was able to conduct analyses using sponsor's code and data. However, there are two issues that need to be considered:

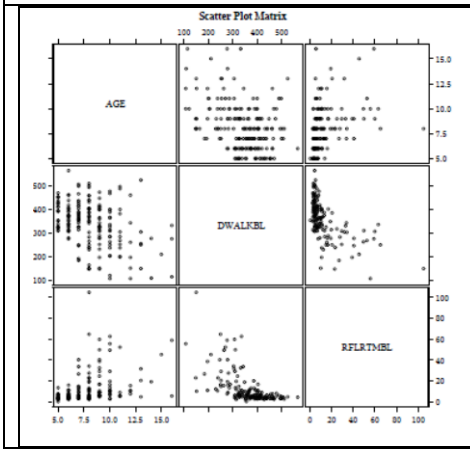
- Acceptability of matching distance measure (6MWD±30m, Age±0.5y).
- Matching analysis using data from patients with various mutations.

Acceptability of matching distance measure (6MWD±30m, Age±0.5y)

Data from the placebo group in DMD114044 study was used to understand the impact of baseline prognostic factors such as age, 6MWD, rise time and use of corticosteroids on DMD disease progression (reflected in 6MWD).

Figure 10 shows the scatter plot and correlation between age, 6MWD and rise time at baseline visit in Study 114044. Figure 10 shows that age, baseline 6MWD and rise time are correlated. For example, patients who have trouble rising from floor have lower walking ability and are older in age. These correlations indicate that one or two out of three prognostic factors are adequate for matching analysis.

Figure 10. (Left) Scatterplot matrix (Right) Correlation Coefficients Between Age (AGE), Baseline 6MWD (DWALKBL) and Rise Time (RFLRTMBL) in Study 114044.

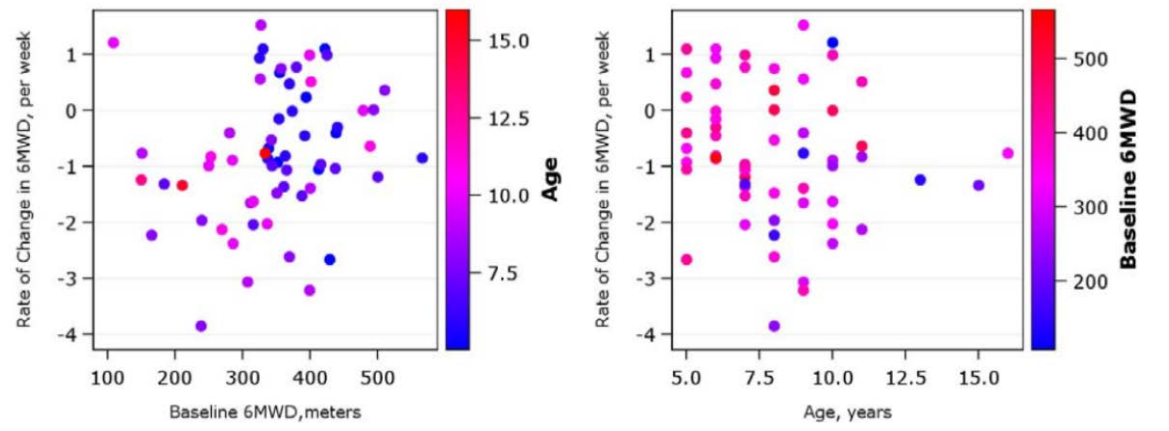


Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	AGE	DWALKBL	RFLRTMBL
AGE Age in years	1.00000 186	-0.38479 <.0001 186	0.37034 <.0001 161
DWALKBL Distance walked baseline (meters)	-0.38479 <.0001 186	1.00000 186	-0.58651 <.0001 161
RFLRTMBL Baseline rise from floor time (seconds)	0.37034 <.0001 161	-0.58651 <.0001 161	1.00000 161

The reviewer estimated rate of change in 6MWD in each DMD114044 study patient using non linear mixed effects analysis. Figure 11 shows the rate of change in 6MWD (per week) by baseline 6MWD and age. Figure 11 suggests that for example, patients with baseline 6MWD of 280 m would have a different trajectory compared to patients with baseline of 350 m. A margin of 30 m would ensure that patients would be reasonably matched as wider margins would group patients with significantly different prognosis. . In addition to 6MWD, it is important that age is also reasonably matched between DMD114673 subjects and natural history. Figure 11 suggests that for example, patients with baseline age of 6 y are less likely to have worse prognosis compared to patients with baseline age of 10 y. Literature also suggests that patients below age of 7 years will have a different progression compared to patients above age of 7 years(Pane, Mazzone et al.). Overall, the sponsor's choice of matching distance measure (6MWD±30m, Age±0.5y) is acceptable (Table 4).

Figure 11. (Left) Relationship Between Rate of Change in 6MWD and Baseline 6MWD (Right) Relationship Between Rate of Change in 6MWD and Baseline Age

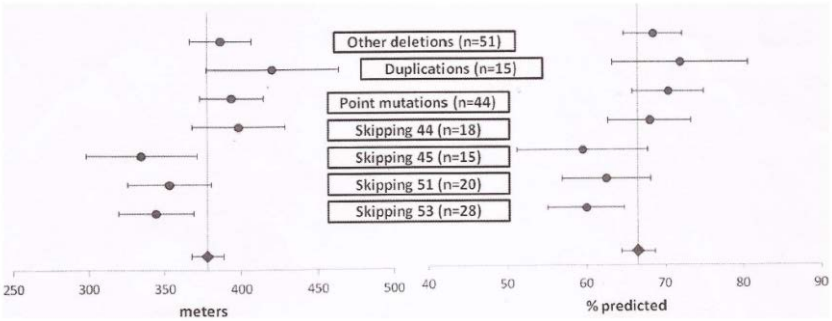


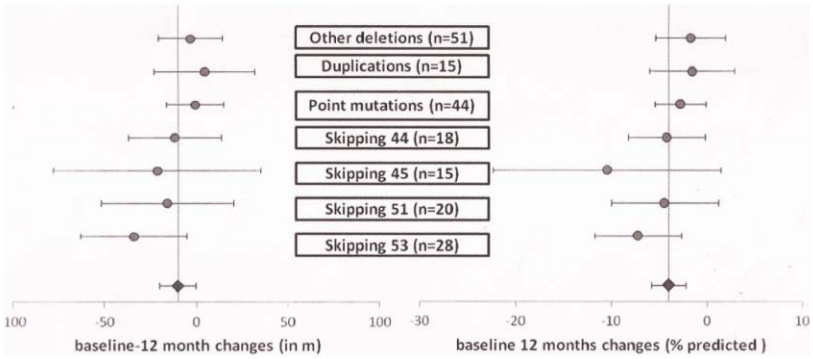
Matching analysis findings using different types of mutations

A recent publication discusses 12 month changes in patients among different types of mutations (deletions, duplications, point mutations) and among subgroups of deletions eligible to skip individual exons. The 6MWT was performed in 191 ambulant DMD boys at baseline and 12 months later (Pane, Mazzone et al.). Figure 12 shows the mean 6MWD data at baseline and change from baseline at the end of 12 months in different types of mutations. The authors concluded that

- Although boys with duplications had better results than those with the other types of mutations, the difference was not significant.
- Similarly, boys eligible for skipping of the exon 44 had better baseline results and less drastic changes than those eligible for skipping exon 45 or 53, but the difference was not significant.
- Even if there are some differences among subgroups, the mean 12 month changes in each subgroup were all within a narrow range from the mean of the whole DMD cohort

Figure 12. (Top) Mean raw scores (left panel) and % predicted (right panel) of 6MWD in individual subgroups. (Bottom) Mean 12 month changes (left panel) and % predicted (right panel) of 6MWD in individual subgroups.





Source: Pane, M., E. S. Mazzone, et al. "6 Minute walk test in Duchenne MD patients with different mutations: 12 month changes." PLoS One **9**(1): e83400.

Reviewer's Comments

- Figure 12 shows that patients with skipping 51 mutations have worse prognosis compared with point mutations or duplications. These differences need to be considered in the matching analysis. Including patients who have better prognosis than patients with skipping 51 mutations will lower the chance of detecting drug benefit.
- While improvements in 6MWD in some DMD114673 study patients could be due to drisapersen, definitive treatment benefit upon long term administration of drisapersen cannot be adequately quantified with the available data. For better interpretation of the data, the sponsor is recommended to

    - Increase the size of natural history data pool, especially from patients with skipping 51 mutations, for matching analysis. While matching analysis using a single natural history database might show drisapersen improves 6MWD, it is possible that matches exist in other databases.

    - Obtain information on presence of LTBP4 (latent transforming growth factor β binding protein 4) and SPP1 (secreted phosphoprotein 1, or

osteopontin) polymorphisms in natural history subjects as well as drisapersen subjects. LTBP4 haplotype is reported to modify age at loss of ambulation(Bello, Kesari et al.).

References

Bello, L., A. Kesari, et al. "Genetic modifiers of ambulation in the Cooperative International Neuromuscular Research Group Duchenne Natural History Study." Ann Neurol **77**(4): 684-96.

McDonald, C. M., E. K. Henricson, et al. (2013). "The 6-minute walk test and other clinical endpoints in duchenne muscular dystrophy: reliability, concurrent validity, and minimal clinically important differences from a multicenter study." Muscle Nerve **48**(3): 357-68.

McDonald, C. M., E. K. Henricson, et al. (2013). "The 6-minute walk test and other endpoints in Duchenne muscular dystrophy: longitudinal natural history observations over 48 weeks from a multicenter study." Muscle Nerve **48**(3): 343-56.

Pane, M., E. S. Mazzone, et al. "Long term natural history data in ambulant boys with Duchenne muscular dystrophy: 36-month changes." PLoS One **9**(10): e108205.

Pane, M., E. S. Mazzone, et al. "6 Minute walk test in Duchenne MD patients with different mutations: 12 month changes." PLoS One **9**(1): e83400.

3 GENOMICS AND TARGETED THERAPY REVIEW

OFFICE OF CLINICAL PHARMACOLOGY
GENOMICS and TARGETED THERAPY GROUP REVIEW

NDA/BLA Number	206031
Submission Date	04/27/2015
Applicant Name	BioMarin Pharmaceuticals
Generic Name	Drisapersen
Proposed Indication	Treatment of Duchenne Muscular Dystrophy
Primary Reviewer	Hobart Rogers Pharm.D, Ph.D.
Secondary Reviewer	Christian Grimstein Ph.D.

EXECUTIVE SUMMARY

Drisapersen is a synthetic antisense oligonucleotide (AON) that is targeted against exon 51 of the dystrophin gene. Drisapersen is being developed for the treatment of Duchenne Muscular Dystrophy (DMD) in individuals who possess deletion mutations amenable to the skipping of exon-51 to restore the reading frame and produce an internally-deleted dystrophin protein. Individuals with these internally-deleted dystrophins have on average a much milder form of disease known as Becker Muscular Dystrophy (BMD). The sponsor is seeking an approval of drisapersen for all mutations amenable to skipping exon-51 in the *DMD* gene, however not all mutations were studied in the clinical trials. The purpose of this review is to evaluate whether drisapersen should be approved for all mutations amenable to exon-51 skipping by drisapersen. The review concluded that given the lack of available subjects for study, coupled with inherent heterogeneity in disease, along with the unknowns regarding the functionality of the internally-deleted dystrophin; determining efficacy in patients with ultra-rare DMD mutations amenable to exon-51 skipping is difficult. Furthermore, there are no reasons to believe that the safety of drisapersen is in any way different in these ultra-rare populations of patients. Hence, it is reasonable to conclude that the restoration of the reading frame by drisapersen should be beneficial for all DMD mutations amenable to exon-51 skipping. The findings of this review indicate that drisapersen, if found to be safe and effective in the studied population, should be indicated for all mutations amenable to exon-51 skipping.

1 Background

Duchenne Muscular Dystrophy (DMD) is characterized by an absence of the protein dystrophin. Dystrophin is a rod shaped cytoplasmic protein that connects the cytoskeleton of a muscle fiber the surrounding extracellular matrix through the cell membrane. Functionally, dystrophin acts to stabilize the sarcolemma membrane against the stress imposed by muscle contraction. The lack of dystrophin in DMD results in a severe disease observed in the first years of life with patients typically losing ambulation around the age of 12 years and the need for mechanical ventilation around 18 years of age. Another related genetic disease is Becker Muscular Dystrophy (BMD), where an internally-deleted dystrophin is produced. BMD results in a much milder phenotype with many patients remaining ambulant throughout life or even asymptomatic. The stark contrast between DMD and BMD phenotype is the presence of dystrophin. In DMD the reading-

frame of the mRNA is disrupted and little to no dystrophin is produced, whereas in BMD, the reading frame is intact and an internally-deleted, but somewhat functional dystrophin protein is produced.

The gene for dystrophin is one of the largest in the human genome consisting of 79 exons. DMD is an X-linked disorder; mutations occur in about 1 in every 3500 male births. There are a large variety of mutations, with one out of three mutations occurring *de novo*. Over 4500 pathogenic mutations are known to cause DMD. Large deletions are present in about 60% of patients, large duplications in about 10% and point mutations (confined mostly to coding exons) in about 30% of patients (PMID: 219693337). Of the deletion mutations, approximately 66% of patients carry a deletion of one or more exons, of which 70% cluster between exon 45 and 55 (PMID: 19156838).

Drisapersen is a synthetic chemically modified 2'-*O*-methyl-phosphorothioate (2OMePS) RNA antisense oligonucleotide composed of 20 nucleotides in a sequence specific for exon 51 of the dystrophin pre-mRNA. Drisapersen binds to exon 51 of the dystrophin pre-mRNA causing exon skipping during processing and restoring the reading frame to produce a truncated internally-deleted dystrophin. In theory, this exon 51 skipping would restore the reading frame of the mRNA to allow an internally-deleted dystrophin protein to be expressed. The resultant protein, while not complete, is expected to convert DMD patients to the less severe BMD phenotype.

2 Submission Contents Related to Genomics

The sponsor submitted the following labeling language for drisapersen:

Indications and Usage:
Drisapersen is an exon skipping oligonucleotide inducer of dystrophin synthesis indicated for the treatment of Duchenne muscular dystrophy (DMD) with mutations in the dystrophin gene that are amenable to treatment with exon 51 skipping as determined by genetic testing.

The sponsor's submitted data included the underlying DMD mutation for all patients. The sponsor's to-be labeled population compared to the studied population will be the focus of this review. The sponsor's proposed labeling states that the drug will be indicated for subjects with mutations in the dystrophin gene that are amenable to treatment with exon 51 skipping as determined by genetic testing.

Of the DMD mutations amenable to treatment with drisapersen, the sponsor has studied nine (17-50, 38-50, 43-50, 45-50, 47-50, 48-50, 49-50, 50, and 52) different DMD deletion mutations in their clinical trials (Table 1).

Table 1. DMD Mutations Present in Placebo-controlled Studies*

	Phase II studies						Phase III study	
	DMD114117			DMD114878			DMD114044	
	Placebo (combined) (N=18)	Drisapersen 6 mg/kg/wk (N=18)	Drisapersen 6 mg/kg intermittent (N=17)	Placebo (combined) (N=16)	Drisapersen 3 mg/kg/wk (N=17)	Drisapersen 6 mg/kg/wk (N=18)	Placebo (N=61)	Drisapersen 6 mg/kg/wk (N=125)
Exon mutation, n (%)								
DMD 43-50 deletion	0	0	0	0	0	1 (6)	0	0
DMD 45-50 deletion	7 (39)	6 (33)	5 (29)	9 (56)	4 (24)	4 (22)	16 (26)	40 (32)
DMD 47-50 deletion	0	0	0	1 (6)	0	0	1 (2)	0
DMD 48-50 deletion	3 (17)	6 (33)	6 (35)	4 (25)	5 (29)	3 (17)	7 (11)	26 (21)
DMD 49-50 deletion	1 (6)	4 (22)	3 (18)	1 (6)	5 (29)	6 (33)	20 (33)	31 (25)
DMD 50 deletion	4 (22)	1 (6)	3 (18)	1 (6)	2 (12)	1 (6)	5 (8)	11 (9)
DMD 52 deletion	3 (17)	1 (6)	0	0	1 (6)	3 (17)	10 (16)	16 (13)
Other	0	0	0	0	0	0	2 (3)	1 (<1)

Source: Derived from Table 22 page 87 module 2.7.3
*One subject with each mutation 17-50, and 38-50 were enrolled as part of the "other" group

3 Key Questions and Summary of Findings

3.1 Are the studied populations in the sponsor's clinical trials representative of the to-be labeled population?

*No. The sponsor has studied nine different DMD mutations amenable to exon-51 skipping therapy. Drisapersen is to be indicated for all mutations amenable to skipping exon 51. Additional DMD mutations (e.g. 19-50, 52-63) are known to exist, however they are ultra-rare (1-2 subjects in database) in nature. A search of the Leiden DMD database (www.dmd.nl) using the known exon splicing (**Figure 1**), identified subjects composing of seven additional DMD mutations (i.e., 3-50, 13-50, 19-50, 29-50, 40-50, 52-58, 52-63) that may be amenable to exon-51 skipping based on the mechanism of action of drisapersen. Amenable mutations are those in which skipping of exon-51 would, in theory, restore the reading frame. For instance, in Figure 1, a subject with a deletion of exons 44-50 would not be amenable to exon-51 skipping as exons 43 and 52 cannot be spliced together, whereas, a deletion of exons 43-50 can be successfully spliced by exon-51 skipping.*

Figure 1. Depiction of the 79 Exons of the Dystrophin Gene and Splicing

Source: PMID 19156838
Note: In-frame exons are in light blue, out-of-frame in dark blue. Deletions are considered in-frame when the exons flanking the deletion "fit."

3.2 ***Should drisapersen be indicated for patients amenable to exon-51 skipping who were not studied in the clinical development program?***

Yes. Despite not all DMD mutations amenable to exon-51 skipping being enrolled in the clinical development program, if drisapersen is ultimately found to be safe and effective to warrant approval, then drisapersen should be indicated for all exon-51 amenable mutations.

Reviewer comment: In theory, restoring the reading frame by skipping exon-51 may result in a milder form of the disease (i.e. transition from DMD phenotype towards a BMD phenotype); therefore it has the potential to be efficacious for patients with all amenable mutations. However, given the ultra-rare occurrence of some exon-51 amenable mutations (e.g. 43-50 deletions) it is exceedingly difficult to find adequate numbers of patients for clinical studies. Moreover, given the strict inclusion criteria for the drisapersen clinical trials, these patients may have been ineligible to participate (e.g. non-ambulatory). Furthermore, given the inherent variability in disease, studying these ultra-rare mutation subsets may be challenging for determining efficacy or lack thereof.

Many unknowns remain in how the internally-deleted dystrophin can impact disease, both in quantity and quality. Successful exon-51 skipping in the case of each DMD deletion mutation would create a different internally-deleted dystrophin protein. For some mutations amenable to exon-51 skipping we have BMD subjects with the same internally-deleted "in-frame" mutations to infer some degree of functionality of that protein (PMID: 25633150, 22102647). Though generally less severe, even within BMD patients there can be a large heterogeneity in disease phenotype (PMIDs: 25633150, 2404853). While in-frame deletions in the proximal regions of the protein (exons 20-40) tend to be milder than those in the distal part (exons 40-55), it is still difficult to predict exactly what the functionality of the skipped dystrophin protein may be (PMIDs: 19156838,16770791,17041910). For example, a case report of a patient missing exons 17-48 only resulted in mild BMD, with the patient being ambulant at 61 years of age (PMID: 2404210). Thus, it is clear that the amount of exons present isn't directly correlated with functionality. Hence, while we can infer some functionality of an exon-51 skipped product, many unknowns remain on how it can affect clinical phenotype.

Given the lack of available subjects for study, coupled with inherent heterogeneity in disease, along with the unknowns regarding the functionality of the internally-deleted dystrophin, determining efficacy in single patients with a specific exon-51 skipping amenable mutation is difficult. Moreover, there are no reasons to believe that the safety of drisapersen is in any way different in these ultra-rare populations of patients. Thus, if drisapersen is approved, any DMD deletions amenable to exon-51 skipping (i.e., theoretical restoration of the reading frame) should be eligible to receive drisapersen.

3.3 **Is there a difference in the functionality of the exon-skipped truncated dystrophin produced by treatment with drisapersen?**

Potentially, however given the significant intra- and inter-subject variation in disease phenotype; it is likely that large numbers of DMD patients with different mutations would need to be studied in order to determine efficacy. Given the small numbers of subjects in the sponsor's submission with specific DMD deletions, numerical comparisons can only be made for a few of the exon-51 skipping amenable groups.

3.3.1 Sponsor's analysis

The sponsor states that *post hoc* analysis of 48-week ambulant, placebo-controlled studies suggested a that the effect of drisapersen was larger in subjects with a single DMD deletion (treatment difference at Week 48: 22.8 metres for DMD 50 deletion, 30.0 metres for DMD 52 deletion) than for subjects with multiple DMD deletions (treatment difference at Week 48: 9.7 metres for DMD 45-50 deletion, –11.7 metres for DMD 48-50 deletion, 12.2 metres for DMD 49-50 deletion. The sponsor argues that given the small numbers in each group, that these findings should be interpreted with caution.
The sponsor also evaluated the change from baseline 6MWD in the phase 2 placebo-controlled studies. The tendency for single DMD deletions to have improved treatment differences was not observed in this subset.

Furthermore, the sponsor demonstrated an increase in exon skip mRNA for each mutation that had at least five subjects. RT-PCR transcripts of mRNA increased regardless of the studied DMD mutation (**Table 2**).

Table 2. Increase in Exon Skip 51 mRNA at Week 48 in Different Mutation Groups After Drisapersen Compared to Placebo in Study DMD114044

Deletion	Placebo			Drisapersen (6 mg/kg/wk)		
	Mean ± SE (SD)	Median	n	Mean ± SE (SD)	Median	n
Exon 52	0.52 ± 0.13 (0.42)	0.4	10	2.40 ± 1.05 (4.08)	0.5	15
Exon 50	1.62 ± 0.62 (1.38)	1.0	5	2.65 ± 0.68 (1.92)	2.0	8
Exon 49-50	1.83 ± 0.46 (1.96)	1.2	18	3.69 ± 0.96 (5.35)	2.4	31
Exon 48-50	0.70 ± 0.30 (0.79)	0.5	7	1.51 ± 0.28 (1.39)	1.2	25
Exon 45-50	1.90 ± 0.53 (2.05)	1.6	15	3.26 ± 1.17 (7.23)	1.6	38
All deletions	1.45 ± 0.22 (1.68)	0.9	56	2.83 ± 0.48 (5.21)	1.6	118

Abbreviations: n= number, SD = standard deviation
Result of skip mRNA product in a.u. by nested PCR and lab-on-chip analysis. Assay not tested for linearity or accuracy. Rare deletions with only one treated subjects (47-50, 38-50, 17-50), and hence no comparative treatments, not shown.

Source: Summary of clin pharm page 37 module 2.7.2

3.3.2 Reviewer's analysis

The sponsor enrolled nine different DMD deletion mutations that were amenable to exon-51 skipping. The goal of drisapersen treatment is to restore the reading frame and

produce a truncated dystrophin protein similar to patients with BMD. While, each DMD mutation amenable to exon-51 skip will produce a different internally-deleted dystrophin, in theory, it is unlikely that an amenable mutation would not respond to treatment with drisapersen. Given the heterogeneity in disease phenotype DMD mutations, it is difficult to ascertain whether differences in DMD mutation affected efficacy. The sponsor's post-hoc analysis indicated that no significant differences in the 6MWD by DMD mutation type were observed. While there may be some differences in functionality of the exon-51 skipped transcripts; restoring the reading frame to produce dystrophin even if it may be different between DMD mutations is warranted.

4 Summary and Conclusions

Drisapersen is being sought for the indication of the treatment of DMD in all mutations amenable to exon-51 skipping. There were nine different DMD mutations represented in the sponsor's clinical trials; however two mutations had only one representative subject (17-50, 38-50). Although drisapersen was not studied in all DMD mutations amenable to exon-51 skipping, it is reasonable to extrapolate efficacy to ultra-rare populations (i.e., mutations with only one or two known subjects), given the inherent variability in disease, and our understanding of the mechanism of action in restoring the reading frame. Last, there are no reasons to believe that the safety of drisapersen is in any way different in these ultra-rare populations of patients. Hence, given the challenges of studying these ultra-rare populations of disease, coupled with the lack of any unique safety concerns, it is reasonable to approve drisapersen for all DMD mutations amenable to exon-51 skipping, if found to be safe and effective in the studied population.

5 Recommendations

It is the finding of this review that drisapersen, if found to be safe and effective to warrant approval, is likely to benefit all mutations amenable to exon-51 skipping and should be labeled accordingly.

Post-marketing studies

None.

5.1 Labeling recommendations

No additional labeling recommendations.
Drisapersen is an exon skipping oligonucleotide inducer of dystrophin synthesis indicated for the treatment of Duchenne muscular dystrophy (DMD) with mutations in the dystrophin gene that are amenable to treatment with exon 51 skipping as determined by genetic testing.