July 30, 2018

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: FDA-2018-D-1636-0001: *Assessment of Pressor Effects of Drugs*

To Whom It May Concern:

Reference is made to the Federal Register notice of May 31, 2018 announcing the availability of the draft guidance entitled, "Assessment of Pressor Effects of Drugs."

Hoffmann-La Roche Inc. (Roche) and Genentech Inc. (a member of the Roche Group) ("Roche/Genentech") are providing comments on the Agency's suggested approach to the systematic characterization of the effect of a drug on blood pressure during drug development.

We would like to thank the Agency for the opportunity to provide comments on this critical area of safety assessment. Should the Agency have questions on any of these points, we would welcome the opportunity to provide clarification.

Sincerely,

Janet Jenkins-Showalter

Janet Jenkins-Showalter
Head, US Regulatory Policy
Genentech Inc.

GENERAL COMMENTS

While we agree with the spirit of the draft guidance with respect to ambulatory blood pressure monitoring (ABPM), we believe that a risk-based approach would better address the concern of potential drug-induced effects on blood pressure (BP) by reserving ABPM investigations "for cause" (e.g., based on mechanism or action, high-risk population, or evidence of a blood pressure effect in early emerging data). Given the trend in drug development towards smaller, more targeted studies in rare subsets of disease and the challenges associated with recruiting patients for these studies, we note that it may be challenging to power such studies to detect blood pressure effects in the 2 to 3mm Hg range.

Per the cited PRECISION-ABPM study's statistical analysis, "a sample size of 117 evaluable patients per arm allowed detection of a 3 mmHg difference between any two treatment groups, with 80% power and at the 0.0167 (=0.05/3) level of significance."[1] Given that phase I non-oncology studies (i.e. healthy volunteer and/or patient tolerability studies) enroll substantially fewer than 100 patients per arm and that early phase oncology studies are typically of single-arm/open label design, it is not clear to us how interpretable ABPM results would be if incorporated into typical early phase studies. If an early phase I study is not large enough to have sufficient power to detect overall blood pressure effect in the 3 mm Hg range, then the scientific value of the resulting blood pressure information from such ABPM studies may not outweigh the additional operational complexity associated with ABPM implementation. We also note that for oncology and other serious non-oncology indications, underlying comorbidities and concomitant medications, along with a lack of adequate controls, among other factors, may make identification and interpretation of small blood pressure increases even more challenging.

Therefore, in the context of these factors, we ask the Agency to consider the following alternatives:

- A unique, per-program risk-based approach could more pragmatically balance the need to monitor blood pressure effects with drug development considerations, particularly for rare disease and oncology studies. We recommend that intensive blood pressure monitoring remain indicated for drugs at higher risk rather than for all drugs to be administered chronically.

- Systematic investigations of blood pressure could be better suited to the post-marketing setting (i.e. such as PRECISION-ABPM). For example, if the benefit/risk assessment, based on cuff BP measurements/cardiovascular outcomes, at time of product registration suggests residual uncertainty on the topic of cardiovascular risk, a post-marketing study may present a more attractive benefit/risk profile for patients participating in ABPM studies. Once an investigational product is approved and the

[1] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM609185.pdf

initial positive benefit/risk profile established, conducting either a sufficiently sized (i.e. such as PRECISION-ABPM) placebo-controlled (if ethical), or active-controlled (if other standard of care treatments exist), study in patients would present patients with an attractive option of being potentially randomized to a known effective treatment (vs. an investigational treatment in the pre-market setting). In addition, a study in the post-marketing setting may avoid some of the study design considerations associated with early phase studies outlined above and be better able to characterize potential risk of increased BP.

SPECIFIC COMMENTS

Section, Line(s)	**Draft Guidance Text**	**Comment/Recommendation**
214-217 **236-238**	*FDA encourages Sponsors to seek further discussion on this issue, including the arguments for and against using a placebo group as the control in ABPM studies.* *Even though early, small studies will not be useful in detecting subgroup effects, an absence of an overall blood pressure effect should provide reassurance that a subset of patients does not have a large blood pressure effect.*	Per the cited PRECISION-ABPM study's discussion, "For ethical reasons, a placebo comparison arm was not feasible since the protocol required all patients and physicians to document that patient had required NSAID treatment for at least 6 months for adequate symptom relief. Therefore, potential changes in BP vs. no treatment are unknown." The ethical issue encountered in PRECISION-ABPM also likely applies to many other disease areas. With the absence of a control (placebo or active control), the interpretability of ABPM data in small early studies will likely be limited. As a result, it will be challenging to assess whether an "overall blood pressure effect" is due to the investigational treatment or due to other factors (i.e. lifestyle) that would normally be mitigated by randomization to a control arm. Therefore, the scientific value of early small ABPM studies without a control group is questionable. As an alternative, each patient can serve as their own control by monitoring changes in blood pressure during and after treatment vs. their pre-treatment baseline.
186-187	*ABPM allows for a more precise measurement of an individual's blood pressure*	The use of ABPM may not necessarily be more precise than a cuff measurement since most ABPM devices use cuffs for the measurements. Further, while we acknowledge that ABPM devices may produce a more accurate reading than cuff measurements by nature of obtaining more frequent data

	than can be achieved through the use of cuff blood pressure measurements.	points, precision cannot be guaranteed unless all tests are done with the same ABPM cuff and read by the same central facility. In addition, interpatient variability in terms of how the device is worn can affect the precision of the readings.
228-229	*In general, the results should be based on the integrated mean (i.e., area under the curve, a time-weighted average of the blood pressure throughout the day).*	We recommend that the Agency revise this section as follows below in red: "In general, the results should be based on the integrated mean (i.e., area under the curve, a time-weighted average of the blood pressure throughout the day), but may be different depending on mechanism of action and expected PK parameters and PD effects of the drug being investigated."
146-150	*When use of clinic blood pressure measurements is appropriate, accuracy can be improved by collecting triplicate measurements of sitting blood pressure in all subjects at baseline (predose), at several visits (at least two visits before the end of the trial), at the end of the interdosing interval (trough measurement; predose), and at*	We suggest that the early, small studies, which are generally conducted under highly standardized conditions as compared to phase II and phase III studies, could include these suggestions for improving accuracy as standard.

	peak concentration. Measurements should be made at least 1 minute apart using the same arm at each visit.	
236-238	*If no blood pressure effect is detected by ABPM in early, small studies, subsequent studies (later phase 2, phase 3) can utilize routine cuff blood pressure measurement monitoring, which would detect large effects in specific individuals.*	Could FDA clarify whether "no blood pressure effect" is intended to ensure that a threshold effect (e.g., 2-3 mmHg) is ruled out? If the FDA intends for Sponsors to rule out a threshold effect, could FDA please clarify the necessary elements expected to ensure an appropriately designed study – e.g., whether there is a specific confidence interval (e.g. upper bound of 95% CI), mean BP value (e.g., 2-3 mmHg systolic), specific endpoints and timing in relation to dosing, PK-effect modeling, etc?

July 30, 2018

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

RE: Docket No. FDA–2018–D–1636
Assessment of Pressor Effects of Drugs, Draft Guidance for Industry

Dear Sir or Madam:

Novo Nordisk Inc. appreciates the opportunity to provide comments to the above-referenced docket on the *Draft Guidance - Assessment of Pressor Effects of Drugs*.

Novo Nordisk is a pioneer in biotechnology, a world leader in diabetes care and holds a leading position within hemostasis management, growth hormone therapy, and hormone therapy for women. Novo Nordisk manufactures and markets pharmaceutical products and services that make a significant difference to our patients, the medical profession, and society.

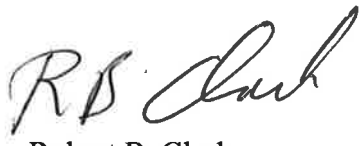
After reviewing the draft guidance, we request clarification or modifications as detailed in the following comments.

Line No.	Comment
General	Please elaborate on the use of home blood pressure measurements over 3 days as an alternative to ABPM. In general ABPM is challenging to use due to expensive equipment, time consuming mounting and de-mounting, data analysis and interpretation and affection of a patients every-day life during the measurement period. Serial in-office, resting cuff measurements during a trial visit or home BP measurements would not be sufficient in a large scale study, which would be much more feasible for sponsors.
21	Please clarify the term “systemic characterization.”
103	The wording "leading to an increase in cardiovascular event rates (Ruschitzka et al. 2017)", is not entirely correct since the sub-study did not demonstrate an increased risk of CV events. Only the main study indicated this increase.
108	Please clarify the need for a thorough evaluation of the PRECISION study within this context.

124	In later part of the guidance it is stated that phase 1/early phase 2 can be the gatekeeper for the need of specific assessment in phase 2-3. However, due to the setting of a phase 1 trial, it might be that one or two individuals will present a minor increase in BP. Therefore, this variable should not be the gatekeeper; other elements such as MOA are as important.
181	We suggest that the guidance clarifies the nomenclature. For example, the term ABPM in the guidance means 24-hour out-of-office measurements. We also request that the guidance quantifies the minimum/maximum interval between individual measurements.
181	The guidance states, “ABPM has several advantages over cuff blood pressure measurements including the following:” Since the ABPM apparatus also uses a cuff, we suggest revising the text to read, “ABPM has several advantages over *in-office* cuff blood pressure measurements including the following: "
184	We recommend that the gold standard blood pressure measurement with cuff, ABMP and HBPM are included in the guideline.
209	It is acknowledged that there can be changes to blood pressure over time that could obscure drug effects, making inclusion of a placebo group desirable, however, there may be situations where a placebo group will not be feasible and it would be a mistake to have inclusion of a placebo group as a general requirement e.g. in disease areas where placebo treatment is not an option and/or unethical.
236	Please clarify which blood pressure measurements are needed in later phase 2 or phase 3 studies when a pressure effect is detected in early small studies.
236	In hemophilia phase 1 trials, there are often low numbers of healthy subjects or patients. In this case, please clarify the number of healthy patients necessary to make a conclusion about a blood pressure increase.
237	We do not agree with the statement in Line 236-7, “If no blood pressure effect is detected by ABPM in early, small studies, subsequent studies (later phase 2, phase 3) can utilize routine cuff blood pressure measurement monitoring, which would detect large effects in specific individuals." The lack of precision can be balanced by large sample sizes (as seen in phase 3 trials) and repeated measures, Therefore, this method is also able to pick up smaller effects on blood pressure. This is critical as it relates to the need for doing ABPM in phase 1. If cuff measurements in phase 3a can pick up relevant signals, please clarify the need for doing ABPM in phase 1.
243	Please clarify the degree of change in mm Hg levels necessary to be considered an increase.
261	A specific increase causing concern across development programs would not take risk tolerance in individual programs into consideration. This is unfortunate because it may stop development therapies where a blood pressure increase could be acceptable e.g. lifesaving therapies.

Thank you for the opportunity to provide comments on the draft guidance. We would be pleased to provide further input or clarification of our comments if needed.

Sincerely,



Robert B. Clark
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August 22, 2018

Division of Dockets Management (HFA–305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: FDA-2018-D-1636 Assessment of Pressor Effects of Drugs; Draft Guidance for Industry

Dear Madam, Sir,

Merck & Co. Inc., Kenilworth, NJ, U.S.A. (the "Company"), is a global research-based pharmaceutical and healthcare company. The Company is known as MSD outside the United States and Canada. Through a combination of the best science and state-of-the-art clinical development, Merck has produced many important medicines and vaccines.

Today the company is actively developing a broad portfolio of small molecules, vaccines and biologic products with the goal of improving worldwide patient access to important and life-saving therapies.

We appreciate the efforts of the FDA to provide guidance to Sponsors on the evaluation of potential pressor effects during the development of new drug candidates. We agree with the overall aims of the draft *Guidance for Industry: Assessment of Pressor Effects of Drugs*; however, we seek further clarity and respectfully provide the following input.

Scope

General: Early discussion is important in any product development program. It would appear that a possible pressor effect study requirement would be based on a particular product characteristics and risk benefit that would be tolerated for a condition. In our opinion, the absolute number with regard to blood pressure increase is not as relevant as how the drug is expected to be used.

Impacted molecule type: It is unclear whether this guidance applies only to small molecules or also applies to biologics.

Impacted therapeutic areas: The issue of short-term administration is addressed. However, it would be helpful to know if there are indications where the drug candidate would be used for chronic use but where life expectancy is limited and therefore the long-term impact on cardiovascular risk may not be a key factor in making a benefit-risk determination (e.g. oncology indications such as metastatic cancers).

Blood pressure lowering effect: The guidance should address situations where a product is shown to have a blood pressure lowering effect. If early studies show that the drug reduces or has no effect on blood pressure, presumably a sponsor would not have to do an ABPM study to rule out an increased blood pressure effect.

Studying supratherapeutic dose: in some ways the effort to define the precision of pressor effects is akin to the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. In this context, is there a role for exposure response analysis in early studies in healthy volunteers at supratherapeutic doses? Given that supratherapeutic doses are quite often achieved in early studies that employ cuff blood pressure measurements, could such an analysis lead to conclusions, for example based on the fact that there is no slope/dose response, that would allow Sponsors to elect not to conduct ABPM? In other words, ruling out a meaningful blood pressure increase at a supratherapeutic dose using a less sensitive tool could obviate the need to use a more sensitive tool at the eventual lower recommended therapeutic dose.

Preclinical Considerations

The draft guidance document does not include preclinical risk assessment. ICH S7A: *Safety Pharmacology Studies for Human Pharmaceuticals* (November 2000) generally recommends that potential effects of drug candidates be conducted preclinically through GLP-compliant safety pharmacology studies of the cardiovascular system to evaluate potential effects of the candidate drug on blood pressure, heart rate and the electrocardiogram. While we acknowledge that there is literature indicating that preclinical studies are not consistently predictive of clinical effects, we recommend that the guidance document address preclinical assessment and that the FDA articulates a position with regard to the de-risking (or lack thereof) that can be achieved through well-designed preclinical studies.

Clinical Threshold

With regard to the relevant clinical threshold to consider in development of drug candidates, due to the many factors involved in the development of a particular drug, we recommend that each development program determine a relevant threshold for effects on blood pressure for a given indication and patient population taking into account factors such as benefits, risks, and patient preferences.

The Guidance contains several examples of drug that produce elevations in blood pressure and were eventually associated with adverse cardiovascular risks. It is noteworthy that the examples were potentially confounded by effects beyond those of increasing blood pressure, so they are of limited value in justifying a minimum clinically meaningful elevation in blood pressure. To our knowledge, the FDA has not issued a guidance that specifies the minimum reduction in blood pressure required to approve a new anti-hypertensive agent. We recognize that the minimum approvable

antihypertensive effect is likely larger than the minimum increase in blood pressure that could be detrimental over a long term. However, it would seem that establishing a regulatory expectation for ruling out a certain increase in blood pressure should be consistent with the amount of flexibility used to evaluate antihypertensive effects.

Study Population

With regard to the population to be studied, there are circumstances where it would be challenging to assess pressor effect in the target disease population and where it may be appropriate to perform the assessment in a population akin to the target population.
We ask the Agency to consider including language in the guidance to this effect.
For Lines 233-234, we would recommend revised wording such as, "Consideration should be made to carrying out the study in a patient population with characteristics similar to the intended target patient population . . ."

Study Sample Size

The document includes statements indicating that small early phase ABPM studies can allow the use of routine cuff blood pressure measurement monitoring in later Phase 2 and Phase 3 (e.g. lines 200-201 and 236). Our initial assessment is that such studies would not be small by Clinical Pharmacology standards (initial power calculations based on the variability observed in some of our internal ABPM studies suggest N ~100 subjects needed for a crossover type design if the difference in SBP to be detected is on the order of 2 mmHg) with healthy subjects. Patient populations are likely to have greater variability in ABPM measurements which would increase N, and an embedded study within a Phase 2a study would likely require a parallel design further increasing the N required. Please provide more clarity around the endpoints expected (24hr DBP vs SBP vs MBP, change from baseline, change from baseline adjusted for placebo), with estimates of the within-subject and total variability for such endpoints as observed in historical data, as well as the statistical criteria to be used to rule out an effect. Alternatively, please provide Sponsors with the guidance that the FDA recognizes that different Sponsors may approach the issue differently, and that the specific design and endpoints should address the specific needs of a given program.

Timing of Study

We appreciate the flexibility of study timing in the guidance document. We request additional information regarding impact on Phase 3 blood pressure assessment. If we observe an increase in blood pressure prior to Phase 3, we believe Phase 3 assessment of blood pressure using cuff sphygmomanometry is adequate if methods are specified and adequate training is done.

Active Control

The guidance is silent on active controls. We believe that an active control should not be necessary in an ABPM study.

Labeling

Information on the anticipated labeling implications of this evaluation of pressor effects would be helpful.

Feedback on FDA's question

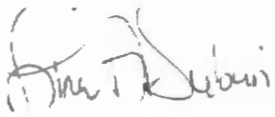
Section	FDA Question	Merck Feedback
Background (Lines 109-110)	*FDA encourages sponsors to seek further discussion on whether the results and interpretation of the PRECISION study are relevant in the context of this guidance.*	We would recommend removing the results and interpretation of the PRECISION study. There are confounding factors in that trial. We are unware of a good example to include in this guidance document.
Control Group (Lines 215-216)	FDA encourages sponsors to seek further discussion on this issue, including the arguments for and against using a placebo as the control in ABPM studies.	If a trial in which ABPM will be assessed includes a placebo control group for other reasons, then ABPM will be assessed in the placebo treatment arm. Otherwise, a placebo arm is not likely needed.
Regulatory Considerations (Lines 262-265)	FDA encourages sponsors to seek further discussion on the best regulatory approach to interpret drug's blood pressure effect including asking the following: Is there a specific, identified increase applied across development programs that is cause for concern, or should each development program have its own threshold as it takes risk tolerance into consideration?	Due to the many factors involved in the development of a particular drug, we recommend allowing each development program to have its own threshold for considering a blood pressure effect as a concern as it takes factors such as patient population, benefits, risks, and patient preferences into consideration.

For Lines 271-274, suggested addition underlined: This assessment should include the consideration of any steps that could be taken to mitigate the risk of increased blood pressure, such as patient selection, pretreatment assessments, blood pressure monitoring

in some or all patients, and planned use of blood pressure-lowering treatments both during clinical development and in post-approval use.

Should you need additional information or wish to hold further discussions with our company representatives, please do not hesitate to contact me at (301) 770-8867 and/or lina.aljuburi@merck.com.

Sincerely,



Lina AlJuburi, PharmD, MS
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