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Paper 34
Date: November 13, 2019

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MALLINCKRODT PHARMACEUTICALS IRELAND LIMITED,
Petitioner,

v.

BIOVIE, INC.,
Patent Owner.

IPR2018-00974
Patent 9,655,945 B2

Before ERICA A. FRANKLIN, MICHELLE N. ANKENBRAND, and KRISTI L. R. SAWERT, *Administrative Patent Judges.*

SAWERT, *Administrative Patent Judge*.

JUDGMENT

Final Written Decision
Determining All Challenged Claims Unpatentable
Denying Patent Owner's Motion to Amend
35 U.S.C. § 318(a)

Granting-In-Part Petitioner's Motion to Strike
37 C.F.R. § 42.5

I. INTRODUCTION

This is a Final Written Decision in an *inter partes* review challenging the patentability of claims 1–14 ("the challenged claims") of U.S. Patent No. 9,655,945 B2 ("the '945 patent," Ex. 1001). We have jurisdiction under 35 U.S.C. § 6, and enter this Decision pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. For the reasons set forth below, we determine that Petitioner has shown, by a preponderance of the evidence, that the challenged claims are unpatentable. *See* 35 U.S.C. § 316(e) (2012). Additionally, we deny Patent Owner's contingent Motion to Amend, and grant-in-part Petitioner's Motion to Strike.

A. Procedural History

Mallinckrodt Pharmaceuticals Ireland Limited ("Petitioner") filed a Petition for an *inter partes* review under 35 U.S.C. § 311. Paper 2 ("Pet."). Petitioner supported its Petition with the Declaration of Dr. Paul Gow. Ex. 1002. BioVie, Inc. ("Patent Owner") filed a Preliminary Response. Paper 6 ("Prelim. Resp.").

On November 14, 2018, pursuant to 35 U.S.C. § 314(a), we instituted trial to determine whether any challenged claim of the '945 patent is unpatentable based on the grounds raised in the Petition:

Claims Challenged	35 U.S.C. §	Reference(s)
1–3, 5	102	Robertson[1]
7, 8, 10	103	Robertson

[1] Marcus Robertson et al., *Continuous Outpatient Terlipressin Infusion for Hepatorenal Syndrome as a Bridge to Successful Liver Transplantation*, HEPATOLOGY 2125–26 (Dec. 2014) ("Robertson," Ex. 1004).

Claims Challenged	35 U.S.C. §	Reference(s)
1, 2, 6, 12	103	Angeli[2]
1–14	103	Fimiani,[3] Robertson
1–14	103	Fimiani, Angeli

Paper 9, 6, 31 ("Institution Decision" or "Inst. Dec.").

Patent Owner filed a Response. Paper 15 ("PO Resp."). Patent Owner supported its Response with the Declaration of Dr. Jaime Bosch. Ex. 2023. Patent Owner also filed a contingent Motion to Amend. Paper 16 ("Motion to Amend" or "Mot. Amend."). Petitioner filed a Reply to Patent Owner's Response (Paper 18, "Pet. Reply"), and an Opposition to Patent Owner's Motion to Amend (Paper 19, "Opp. Mot. Amend."). Patent Owner filed a Sur-reply (Paper 21, "PO Sur-reply"), and a Reply in support of its Motion to Amend (Paper 22, "Reply Mot. Amend."). Patent Owner's Sur-reply was accompanied by a Supplemental Declaration of Dr. Bosch. Ex. 2044. Petitioner filed a Sur-reply to Patent Owner's Reply. Paper 25 ("Sur-reply Mot. Amend.").

On our authorization (Paper 26), Petitioner filed a Motion to Strike (Paper 28, "Mot. Strike"), to which Patent Owner filed an Opposition (Paper 29, "Opp. Mot. Strike").

An oral hearing was held on August 12, 2019. A transcript of the hearing is included in the record. Paper 30 ("Tr."). After the hearing, and

[2] Paolo Angeli, *Terlipressin for the treatment of hepatorenal syndrome in patients with cirrhosis*, 1 EXPERT OPIN. ORPHAN DRUGS 241–48 (2013) ("Angeli," Ex. 1005).

[3] Basilio Fimiani et al., *The use of terlipressin in cirrhotic patients with refractory ascites and normal renal function: A multicentric study*, 22 EUR. J. INTERN. MED. 587–90 (2011) ("Fimiani," Ex. 1006).

on our authorization (Paper 31), Patent Owner filed a Notice of Supplemental Authority (Paper 32, "PO Notice"), to which Petitioner filed a Reply (Paper 33, "Pet. Reply to Notice").

B. Real Parties in Interest

Petitioner identifies its real parties-in-interest as Mallinckrodt Pharmaceuticals Ireland Limited and Mallinckrodt Hospital Products Inc. Pet. 3. Patent Owner identifies its real party-in-interest as BIOVIE, Inc. Paper 4, 2.

C. Related Matters

According to the parties, there are no pending judicial proceedings involving the '945 patent. Pet. 3; Paper 4, 2. Petitioner states that U.S. Patent Application No. 15/491,613 is related to the '945 patent and is currently pending before the Office. Pet. 3.

D. The '945 Patent

The '945 patent, titled "Treatment of Ascites," issued on May 23, 2017. Ex. 1001, code (45). The '945 patent relates to "a method for treating ascites patients by administering the peptide drug terlipressin." *Id.* at 1:14–15.

According to the '945 patent, "[a]scites is a frequent and life-threatening complication of advanced liver cirrhosis with an expected 40% mortality rate within two years of diagnosis." *Id.* at 1:18–20. Although there is no FDA-approved drug for treating ascites, diuretics are administered off-label "with limited and temporary efficacy." *Id.* at 1:20–23. As liver cirrhosis progresses, however, a patient's ascites may become refractory (i.e., unmanageable) with diuretics. *Id.* at 1:26–28.

Patients suffering from refractory ascites may also develop hepatorenal syndrome (HRS)—another complication of advanced liver cirrhosis that marks the beginning of renal failure. *Id.* at 2:26–28. There are two types of HRS: type 1 (HRS-1) and type 2 (HRS-2). *Id.* at 2:43–46. HRS-1 is more severe than HRS-2, and thus, HRS-1 patients require hospitalization, whereas HRS-2 patients are ambulatory. *Id.* at 2:42–45.

The ’945 patent states that HRS-1 patients have been successfully treated with intravenous (IV) injections of terlipressin every 4 to 6 hours. *See id.* at 1:23–26 (stating that terlipressin has been used to “save their lives”). The ’945 patent also states, “investigational studies have shown that IV injections of terlipressin every 4 to 6 hours in combination with diuretics may resolve refractory ascites in hospitalized patients and decrease the need for large volume paracentesis (ascites fluid withdrawal by needle).” *Id.* at 1:28–33. These high-dose IV injections, however, “carry a high risk of side effects.” *Id.* at 1:33–34. The ’945 patent states that “[m]ore recent studies with hospitalized HRS patients indicate that a continuous infusion of terlipressin can achieve similar efficacy to intermittent injections with a much better safety profile.” *Id.* at 1:34–37. But “to date there have been no published studies of using a continuous low-dose infusion terlipressin to manage ascites in non-hospitalized patients with cirrhosis.” *Id.* at 1:37–40.

The ’945 patent states that the present inventors “have identified a need in the art for a method to treat ascites patients on an outpatient basis and potentially avoid or delay the need for hospitalization due to HRS or other life-threatening complications.” *Id.* at 1:41–44. In one embodiment, terlipressin may be administered continuously by a pump at a dosage range of about 0.5 gm to about 20 mg every 24 hours, for a period from about one

day to about 12 months or more. *Id.* at 2:67–3:17. The '945 patent states that the presence, progression, or improvement of disease may be determined by measuring one or more of the following factors: serum creatinine concentration, plasma sodium concentration, urinary sodium excretion, and urea concentration in serum. *Id.* at 3:36–40. A reduction in serum creatinine concentration, for example, indicates an improvement in renal function, which in turn "indicates an improvement in disease condition." *Id.* at 3:40–46.

The '945 patent provides two examples of patient groups with ascites: one prophetic group to be treated with continuous infusion pump terlipressin therapy (Example 1), and one group actually treated with continuous infusion pump terlipressin therapy (Example 2). *Id.* at 4:6–7:40. In Example 1, the '945 patent states that 15 subjects having ascites but not HRS "will be administered continuous low dose (escalating from 2.0 to 3.0 mg per 24 hours) terlipressin via ambulatory infusion pump." *Id.* at 4:11–15. The '945 patent states that "[t]hese patients are expected to experience a decrease [in] the severity of ascites and the accumulation of ascites fluid over the course of treatment," as well as other health benefits. *Id.* at 4:15–27. Thus, "continuous infusion pump (CIP) terlipressin represents a potentially life-saving solution for these seriously ill patients who are still ambulatory (have not yet been administered [sic] to the hospital for treatment) and have not developed type 1 or type 2 HRS." *Id.* at 4:27–31.

E. Illustrative Claims

Of the challenged claims, claims 1 and 7 are independent and illustrative of the claimed subject matter. Claim 1 recites:

> 1. A method for treating a patient diagnosed with ascites due to liver cirrhosis, the method comprising administering terlipressin or salt thereof as a continuous infusion dose of about 1.0 mg to about 12.0 mg per day to the patient for about one day to about 12 months.

Ex. 1001, 8:25–29. Claim 7 recites:

> 7. A method for reducing the accumulation of ascitic fluid in the abdominal cavity in an ambulatory ascites patient, the method comprising administering to the patient terlipressin or salt thereof as a continuous infusion dose of about 1.0 mg to about 12.0 mg per day for about one day to about twelve months with an ambulatory infusion pump.

Id. at 8:42–47.

II. PETITIONER'S MOTION TO STRIKE

Petitioner's moves to strike Exhibit 2044 and the portions of Patent Owner's Sur-Reply (Paper 21) that cite to, or rely on, Exhibit 2044, from the record in this proceeding. Mot. Strike 1. Exhibit 2044 is a Supplemental Declaration of Dr. Bosch, Patent Owner's declarant, filed in support of Patent Owner's Sur-Reply. Petitioner contends that Patent Owner's filing of Exhibit 2044 is contrary to the Board's instructions in the August 2018 Update to the PTAB Trial Practice Guide ("2018 Trial Guide Update"),[4] which states that a sur-reply "may not be accompanied by new evidence

[4] *See* 83 Fed. Reg. 38,989 (Aug. 13, 2018) (notifying the public of the updated "Practice Guide" and its accessibility through the USPTO website: https://go.usa.gov/xU7GP).

other than deposition transcripts of the cross-examination of any reply witness." *Id.*

Patent Owner responds that we should permit the Supplemental Declaration under the 2018 Trial Guide Update because "expert testimony 'is generally permitted where the expert's scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue.'" Opp. Mot. Strike 1 (quoting 2018 Trial Guide Update, 2). And here, Patent Owner argues, Dr. Bosch's Supplemental Declaration serves "to explain and respond to scientific and technical arguments in [Petitioner's] Reply to Patent Owner's Response." *Id.* at 2. Citing *ResMed Ltd. v. Fisher & Paykel Healthcare Ltd.*, IPR2016-01724, -01735, Paper 25 (PTAB Sept. 28, 2017), Patent Owner also argues that the Board "has permitted a patent owner to submit short, supporting expert declarations with sur-replies to respond to arguments in petitioner's reply briefs that included supporting expert declarations containing new evidence," and should do so in this case as well. *Id.* at 2–3. Finally, Patent Owner argues that we should deny Petitioner's Motion to Strike because "'striking . . . a portion of a party's brief is an exceptional remedy that the Board expects will be granted rarely.'" *Id.* at 3 (quoting 2018 Trial Guide Update, 18).

The 2018 Trial Guide Update explains that a "sur-reply may not be accompanied by new evidence other than deposition transcripts of the cross-examination of any reply witness. Sur-replies should only respond to arguments made in reply briefs, comment on reply declaration testimony, or point to cross-examination testimony." 2018 Trial Guide Update, 14.

Further, the 2018 Trial Guide Update explains that a "sur-reply that raises a new issue or belatedly presents evidence may not be considered." *Id.* at 15.

Thus, we agree with Petitioner that Patent Owner's submission of Exhibit 2044 does not follow the procedure set forth in the 2018 Trial Guide Update, which prohibits new evidence submitted with a sur-reply. *Id.* at 14. Although Patent Owner is correct that the Board has allowed a patent owner to file additional evidence with a sur-reply, it has done so when the Patent Owner sought authorization to file the additional evidence in the first place. *See ResMed Ltd.*, Paper 25 at 3. Here, Patent Owner did not seek authorization from the Board to file additional evidence with its Sur-reply. We agree with Petitioner, therefore, that Patent Owner improperly relies upon Exhibit 2044 in its Sur-reply.

Accordingly, we strike the following portions of Patent Owner's Sur-reply as follows:

- Page 1 – "This Sur-Reply is supported by the Supplemental Declaration of Dr. Jaime Bosch (Ex. 2044)";
- Page 11 – "Ex. 2044, ¶7" and the following "*Id.*";
- Page 16 – "Ex. 2044, ¶¶8-11";
- Page 20 – "Ex. 2044, ¶6";
- Page 22 – "Ex. 2044, ¶14," "Ex. 2044, ¶¶15-17," and "Ex. 2044, ¶18."

We decline, however, to strike Exhibit 2044 from the record. Patent Owner properly relies on Exhibit 2044 in its Reply in support of its Motion to Amend. We determine that the better course of action is to disregard Patent Owner's reliance on Exhibit 2044 as to Petitioner's challenges to the patentability of claims 1–14, but not as to the patentability of the proposed

substitute claims. *See* 2018 Trial Guide Update, 17 (explaining that "the Board is capable of identifying new issues or belatedly presented evidence when weighing the evidence at the close of trial, and disregarding any new issues or belatedly presented evidence that exceeds the proper scope of reply or sur-reply"). For these reasons, Petitioner's Motion to Strike is granted in part.

III. PATENTABILITY ANALYSIS

We have reviewed the parties' respective briefs as well as the relevant evidence discussed in those papers. For the reasons discussed in detail below, we determine that Petitioner has shown by a preponderance of the evidence that claims 1–3 and 5 of the '945 patent are unpatentable under 35 U.S.C. § 102 as anticipated, and that claims 1–14 are unpatentable under 35 U.S.C. § 103 as having been obvious.

A. Principles of Law

To prevail in its challenges to the patentability of all claims of the '945 patent, Petitioner must demonstrate by a preponderance of the evidence that the claims are unpatentable. 35 U.S.C. § 316(e) (2012); 37 C.F.R. § 42.1(d) (2017). "In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable." *Harmonic Inc. v. Avid. Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016); *see also* 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify "with particularity . . . the evidence that supports the grounds for the challenge to each claim"). That burden of persuasion never shifts to Patent Owner. *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015); *see also In re Magnum Oil Tools*

Int'l, Ltd., 829 F.3d 1364, 1375–78 (Fed. Cir. 2016) (discussing the burden of proof in *inter partes* review).

A claim is anticipated and, therefore, unpatentable under 35 U.S.C. § 102, if all of its limitations are disclosed either explicitly or inherently in a single prior-art reference. *In re Schreiber*, 128 F.3d 1473, 1477 (Fed. Cir. 1997). That single prior art reference must disclose all the limitations of the claim "arranged or combined in the same way as in the claim." *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1370 (Fed. Cir. 2008).

A claim is unpatentable for obviousness if, to one of ordinary skill in the pertinent art, "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made." 35 U.S.C. § 103(a) (2006); *see also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including the scope and content of the prior art, any differences between the claimed subject matter and the prior art, the level of ordinary skill in the art, and objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). A petitioner cannot satisfy its burden of proving obviousness by employing "mere conclusory statements." *Magnum Oil*, 829 F.3d at 1380. Moreover, a decision on the ground of obviousness must include "articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR*, 550 U.S. at 418 (citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)).

We analyze Petitioner's asserted grounds of unpatentability in accordance with the above-stated principles.

B. Level of Ordinary Skill in the Art

We consider the asserted grounds of unpatentability in view of the understanding of a person of ordinary skill in the art, and thus begin with the level of ordinary skill in the art. The ordinarily skilled artisan is a "legal construct" that "presumes that all prior art references in the field of the invention are available to this hypothetical skilled artisan." *In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998).

Petitioner contends, and Patent Owner does not dispute, that the relevant "time of the invention" in this case is July 30, 2015—the earliest filing date in the priority chain for the '945 patent. Pet. 19; *see generally* PO Resp. As of that time, Petitioner contends that an ordinarily skilled artisan:

> was typically a person who had a Ph.D. in the areas of pharmacy, chemistry, biochemistry, or a related discipline, or a M.D. specializing in hepatology, internal medicine, and/or gastroenterology, and at least 5 years of experience treating patients with ascites due to liver cirrhosis and at least 3 years administering vasoconstrictors such as terlipressin for the treatment of patients diagnosed with liver cirrhosis.

Pet. 19–20; Ex. 1002 ¶ 25. Petitioner also contends that the ordinarily skilled artisan "would also be well versed in the relevant technical publications and be experienced in various routes of administration of drugs to treat ascites." Pet. 20; *see also* Ex. 1002 ¶¶ 23–26.

Patent Owner agrees with Petitioner that an ordinarily skilled artisan "could have either an M.D. or a Ph.D. in a relevant field, with at least several years of experience in their field." PO Resp. 4 (citing Ex. 2023 ¶¶ 28–30). Patent Owner also agrees that the ordinarily skilled artisan "should have exposure to the administration of vasoconstrictor agents for the

treatment of patients diagnosed with cirrhosis," but disagrees with Petitioner that the skilled artisan necessarily "would have had direct experience with those agents." *Id.*

Patent Owner argues that, although the ordinarily skilled artisan "would be well-versed in the technical publications relating to drugs to treat ascites," as Petitioner contends, that artisan "would have understood that, at the time of the invention, none of the agents used to treat ascites was administered routinely as a continuous infusion." *Id.* (citing Ex. 2023 ¶ 30). Patent Owner also argues that an ordinarily skilled artisan "would have understood that treating ascites is not the same as treating hepatorenal syndrome ('HRS') or improving renal function." *Id.* (citing Ex. 2023 ¶ 30).

At institution, we preliminarily adopted Petitioner's definition of an ordinarily skilled artisan, and also determined that the prior art itself was sufficient to demonstrate the level of ordinary skill in the art at the time of the invention. Inst. Dec. 8. For this Decision, we maintain that the prior art demonstrates the appropriate level of ordinary skill in the art. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (the prior art, itself, can reflect appropriate level of ordinary skill in art).

Nevertheless, for further clarity, we set forth the definition of an ordinarily skilled artisan as follows. As to level of education, we agree with the parties that an ordinarily skilled artisan would have had either a doctorate degree (Ph.D.) in a scientific discipline such as pharmacology, chemistry, and/or biochemistry, or a medical degree (M.D.), with specialization in hepatology, internal medicine, and/or gastroenterology. Ex. 2023 ¶¶ 28–29; Ex. 1002 ¶ 25. We also find that the ordinarily skilled artisan would have had several years' experience in their relevant fields, but

disagree with Petitioner that an ordinarily skilled artisan necessarily would have had direct experience treating patients with ascites, or with administering terlipressin. In this regard, we find credible Dr. Bosch's statement that an ordinarily skilled artisan's "exposure to [terlipressin] could have come from a review of the literature on others' experience with such administration." Ex. 2023 ¶ 29. We otherwise find no substantive difference between the parties' respective proposed definitions of a person of ordinary skill, and find that the outcome of this case would be the same regardless of which definition is used.

We acknowledge Patent Owner's assertions that an ordinarily skilled artisan "would have understood that, at the time of the invention, none of the agents used to treat ascites was administered routinely as a continuous infusion" and "would have understood that treating ascites is not the same as treating hepatorenal syndrome ('HRS') or improving renal function." PO Resp. 4. But we conclude that these statements go to the scope and content of the prior art under *Graham*, and thus, are best addressed in relation to Petitioner's asserted grounds of unpatentability based on obviousness.

Finally, we consider each party's declarant—Dr. Gow and Dr. Bosch—qualified to opine as to the perspective of an ordinarily skilled artisan at the time of the invention. *See* Ex. 1003 (Dr. Gow's curriculum vitae); Ex. 2024 (Dr. Bosch's curriculum vitae).

C. Claim Construction

Having defined the ordinarily skilled artisan, we now turn to claim construction. For petitions filed before November 13, 2018[5]—as here—the Board interprets claims in an unexpired patent using the "broadest reasonable construction in light of the specification of the patent." 37 C.F.R. § 42.100(b) (2017); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). Under that standard, we presume that a claim term carries its "ordinary and customary meaning," which "is the meaning that the term would have to a person of ordinary skill in the art in question" at the time of the invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). We need not explicitly interpret every claim term for which the parties propose a construction. *See* 35 U.S.C. § 314(a) (2012); *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) ("[O]nly those terms need be construed that are in controversy, and only to the extent necessary to resolve the controversy."); *see also Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (applying *Vivid Techs.* in the context of an *inter partes* review).

1. The preamble of claim 1

The preamble of claim 1 recites "[a] method for treating a patient diagnosed with ascites due to liver cirrhosis." Ex. 1001, 8:25–26.[6]

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[5] *See* Changes to the Claim Construction Standard for Interpreting Claims in Trial Proceedings Before the Patent Trial and Appeal Board, 83 Fed. Reg. 51,340 (Oct. 11, 2018) (amending 37 C.F.R. § 42.100(b) effective November 13, 2018 to require a federal district court claim construction approach) (now codified at 37 C.F.R. § 42.100(b) (2019)).

[6] Before institution, Petitioner argued that the preamble is not limiting. *See* Pet. 11–12 (contending that the "preamble of claim 1 is merely a

Petitioner contends that the preamble should be broadly construed to encompass administering terlipressin for *any* reason, because "the preamble does not limit the claim to the treatment of ascites itself." Pet. 12. Patent Owner argues that the preamble limits the scope of claim 1 to treating a patient *for* ascites. PO Resp. 6–15; PO Sur-reply 2–5.

We begin with the words of the preamble. *See Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 457 F.3d 1293, 1301 (Fed. Cir. 2006) ("claim construction must begin with the words of the claims themselves"). We observe that the plain language of the preamble requires treating a patient *diagnosed with* ascites due to liver cirrhosis, but does not require treating ascites due to liver cirrhosis in the patient. Ex. 1001, 8:25–26. Therefore, we agree with Petitioner that the words of the preamble themselves do not limit the claim to the treatment of ascites itself.

We now turn to the intrinsic record. Patent Owner argues that the intrinsic record "makes clear that the point of the claimed method . . . was to actually treat the patient's ascites." PO Resp. 7–8. And thus, Patent Owner argues, "[t]he broadest *reasonable* construction would require that the claimed method of 'administering' terlipressin actually treat (i.e., improve) the patient's ascites (i.e., treating ascites in a patient diagnosed with ascites due to liver cirrhosis)." *Id.* at 8.

Patent Owner points to portions of the specification describing the prior-art administration of terlipressin to HRS-1 patients. *See* PO Resp. 8–9

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statement of intended use"). In our Institution Decision, we determined that the preamble is limiting because it provides antecedent basis for the term "the patient" in the body of the claim. Inst. Dec. 9–10. After institution, Petitioner states that it "assumes the preamble is limiting," and no longer challenges our determination. Pet. Reply 3 n.1.

(citing Ex. 1001, 2:50–59; Ex. 1002 ¶¶ 35, 55; Ex. 2023 ¶¶ 76–81). Patent Owner argues that an ordinarily skilled artisan would have understood, based on the prior art cited, that "continuous infusion terlipressin had already been used in patients with ascites due to liver cirrhosis." *Id.* (citing Ex. 1002 ¶¶ 74–75; Ex. 2023 ¶ 80). Given these disclosures, Patent Owner argues, "it is not reasonable to construe the term 'treating a patient diagnosed with ascites due to liver cirrhosis' as only requiring treatment of a patient *diagnosed* with ascites due to liver cirrhosis." *Id.* at 9. Instead, the broadest reasonable interpretation "would recognize the specification's numerous statements that make clear that the invention relates, in one aspect, to the use of continuous infusion terlipressin to *treat* ascites." *Id.* at 9–11. As further support, Patent Owner cites to the title of the '945 patent, *id.* at 10 (citing Ex. 1001, 1:1 "Treatment of Ascites"), as well as numerous passages and two examples in the written description referring to the treatment and management of ascites in patients, *id.* at 9–11 (citing Ex. 1001, 1:19–20, 1:37–40, 1:28–33, 2:40–50, 4:7–31 (Example 1), 4:33–7:41 (Example 2)).

Patent Owner also argues that, during prosecution, "both the Applicant and the Examiner . . . treated the preamble as requiring the terlipressin to actually treat the ascites." *Id.* at 14. As support, Patent Owner points to applicant's statements, made during prosecution, that the claims "recite methods for the treatment of ascites" and "are directed to the use of terlipressin as a treatment for ascites." *Id.* at 13 (quoting Ex. 1008, 307–308). Patent Owner argues that, over the course of prosecution, the Examiner modified her prior-art rejections "to identify where the art allegedly teaches that terlipressin treats ascites." *Id.* at 13–14 (citing Ex. 1008, 326–27, 330, 333–34).

We recognize that the broadest reasonable interpretation "is an interpretation that corresponds with what and how the inventor describes his invention in the specification." *In re Smith Int'l, Inc.*, 871 F.3d 1375, 1383 (Fed. Cir. 2017). And here, it is true that the title of the '945 patent recites "treatment of ascites," Ex. 1001, code (12), and the written description of the patent consistently recites "treating ascites" and "manag[ing] ascites," *see, e.g.*, *id.* at 1:19–20, 37–40. It is also true that, during prosecution, the applicant and the Examiner characterized the claims as directed to the use of terlipressin as a treatment for ascites. *See*, *e.g.*, Ex. 1008, 308, 326–27, 330, 333–34. Nevertheless, the plain language of the preamble unambiguously recites a method "for treating a patient *diagnosed with* ascites." Ex. 1001, 8:25–26 (emphasis added). It does not recite the more common verbiage of, for example, a method for treating a particular disease—i.e., ascites. For example, we contrast claim 1 with claim 7, the latter of which makes clear that the claimed method is "*for* reducing the accumulation of ascitic fluid in the abdominal cavity in an ambulatory ascites patient." *Id.* at 8:42–43 (emphasis added).

The Federal Circuit has explained that, in cases where the "claim language has as plain a meaning on an issue" that the language "leav[es] no genuine uncertainties on interpretive questions relevant to the case, it is particularly difficult to conclude that the specification reasonably supports a different meaning." *Straight Path IP Grp., Inc. v. Sipnet EU S.R.O.*, 806 F.3d 1356, 1361 (Fed. Cir. 2015). Here, even if the applicant intended for the preamble to recite a method for treating ascites, the plain words of the preamble do not reflect that intention. We may not use the intrinsic record as a basis for adopting an interpretation of the preamble that is contrary to its

plain language, because "[i]n claim construction, [the Federal Circuit] gives primacy to the language of the claims, followed by the specification." *Tempo Lighting, Inc. v. Tivoli, LLC*, 742 F.3d 973, 977 (Fed. Cir. 2014). This rule applies even if the plain language reads on the prior art. *See, e.g.*, *Tate Access Floors, Inc. v. Interface Architectural Res., Inc.*, 279 F.3d 1357, 1372 (Fed. Cir. 2002) ("where claim language is clear we must accord it full breadth even if the result is a claim that is clearly invalid").

Moreover, this is not a case where the *breadth* of a particular term is at issue. In *Smith International*, for example, the Federal Circuit held that the Board's interpretation of the claim term "body" was unreasonably broad because that interpretation did not correspond with the specification's repeated and consistent descriptions of "body" as a component distinct from other components, such as "mandrel" and "piston." 871 F.3d at 1382. Our decision here is not about the breadth of any one particular claim term, but rather, is based on the particular order of claim terms. Put differently, the preamble unambiguously recites "treating a patient," instead of treating a particular disease, and thus, the order of words themselves do not limit the preamble to treating ascites. Ex. 1001, 8:25–26; *see also In re Hyatt*, 708 F.2d 712, 714 (Fed. Cir. 1983) ("A claim must be read in accordance with the precepts of English grammar.").

We also maintain the reasoning from our Institution Decision that certain passages of the written description support an interpretation of the preamble not limited to the treatment of ascites itself. *See* Inst. Dec. 11–12. Specifically, the '945 patent states that the disclosed method "can improve renal function in an ascites patient" and "can be used for reducing the risk of spontaneous bacterial peritonitis, improving the Model for End-Stage Liver

Disease (MELD) score of an ascites patient and/or correcting hyponatremia in an ascites patient." Ex. 1001, 3:19–26; *see also id.* at 1:60–2:14 (disclosing a method for improving renal function in an ascites patient, a method for correcting hyponatremia in an ascites patient, a method for improving the health status of the ascites patient, and a method of improving the Model for End-Stage Liver Disease (MELD) score of an ascites patient.)

In response, Patent Owner argues that, in every passage disclosing the treatment of other conditions—e.g., renal function, hyponatremia, and hepatitis C—the written description makes clear that those treatments are in addition to the treatment of ascites itself because the methods are performed on an "ascites patient." PO Sur-reply 2–4 (citing Ex. 1001, 1:60–2:13, 3:19–34). Thus, Patent Owner argues, "simply because the claims may include treating a disease/condition other than ascites does not lead to the conclusion that the claims may be interpreted as treating the other disease/condition *but not ascites*." *Id.* at 5.

Although we agree with Patent Owner that the '945 patent recites treating those conditions in an "ascites patient," we decline to interpret the preamble as requiring the treatment of both ascites and a separate condition. Again, the plain language of the preamble requires treatment in a patient diagnosed with ascites, but does not require treatment for ascites. Ex. 1001, 8:25–26; *see Chef Am., Inc. v. Lamb-Weston, Inc.*, 358 F.3d 1371, 1374 (Fed. Cir. 2004) ("[I]n accord with our settled practice we construe the claim as written, not as the patentees wish they had written it.").

For the above reasons, we interpret the preamble to encompass treating a patient diagnosed with ascites due to liver cirrhosis for any reason, not limited to the treatment of ascites itself.

2. Claim 12 recitation of "patient"

Claim 12 depends from claim 1, and recites "wherein patient has not progressed to HRS type 1." Ex. 1001, 8:57–58; *see also* Cert. of Correction (correcting "FIRS" to "HRS"). Patent Owner argues that the term "patient" in claim 12 should be read as "the patient," because "patient" without the definite article "the" is an obvious typographical error. PO Resp. 15 (*citing CBT Flint Partners, LLC v. Return Path, Inc.*, 654 F.3d 1353, 1358 (Fed. Cir. 2011)). Petitioner does not dispute this construction. *See generally* Pet. Reply. We note that all other claims dependent (either directly or indirectly) on claim 1 and referring to a patient, recite "the patient." *See* Ex. 1001, 8:35–36 (claim 4), 8:59–60 (claim 13). Thus, we agree with Patent Owner that the recitation of "patient" rather than "the patient" in claim 12 is an obvious typographical error, and read the claim as reciting "the patient."

3. Other claim terms

Based on our review of the record, we determine that no other claim term requires an express interpretation to resolve the issues presented by the Petitioner's patentability challenges. *See Vivid Techs.*, 200 F.3d at 803.

D. Asserted References

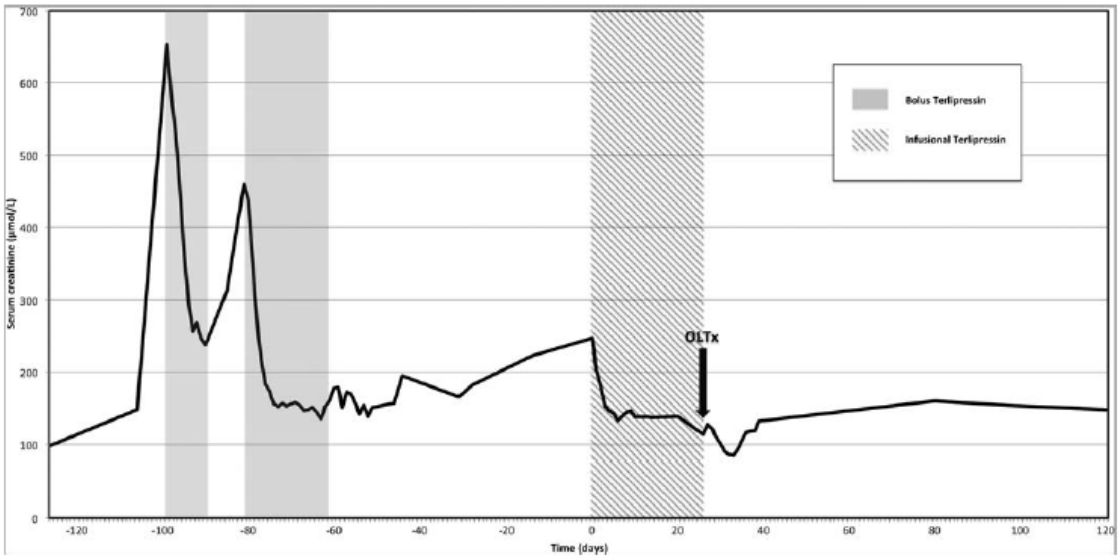
Before turning to Petitioner's asserted grounds of unpatentability, we provide a brief summary of the asserted references.

1. Robertson

Robertson provides a case study of "an outpatient continuous terlipressin infusion for treatment of recurrent HRS as a bridge to successful liver transplantation." Ex. 1004, 2125. Robertson describes the studied patient as having "Child-Pugh C cirrhosis due to previous alcohol consumption complicated by recurrent encephalopathy, diuretic-resistant

ascites, and hepatocellular carcinoma." *Id.* The patient was treated with an infusion of 3 mg terlipressin delivered by a "GemStar pump." *Id.* Robertson states that the patient was initially treated on an inpatient basis, but after the sixth day, "the patient was discharged home with an ambulatory terlipressin infusion." *Id.* The treatment continued for 22 days, at which point the patient underwent a liver transplant. *Id.*

Figure 1 of Robertson, reproduced below, provides the patient's serum creatinine levels both before and after transplantation. *Id.* at 2126.



> Figure 1 provides serum creatinine levels (μmol/L) pre- and post- liver transplant (OLTx). Before the transplant, the patient was treated with both bolus terlipressin and infusional terlipressin. Ex. 1004, 2126.

Before the transplant, the patient's serum creatinine levels were managed by administration of bolus terlipressin, shown by the solid gray highlighted areas in Figure 1, and by infusional terlipressin, shown by the striped gray highlighted area. *Id.* at 2125. At 10 days post-transplantation, the patient's serum creatinine level was 117 μmol/L. *Id.* Robertson states that these results "illustrate[] the successful use of a continuous outpatient terlipressin

infusion in a patient with type 1 HRS over a 4-week period as a bridge to liver transplantation." *Id.* at 2126. Further, "outpatient terlipressin is feasible, and in this case efficacious and well tolerated." *Id.*

2. Angeli

Angeli provides an overview on the use of terlipressin for the treatment of HRS in patients with cirrhosis. Ex. 1005, 241. Angeli explains that the main pathophysiological feature of HRS is renal arterial vasoconstriction, "which is the extreme renal functional abnormality that can occur in patients with cirrhosis and ascites." *Id.* Terlipressin, a vasoconstrictor, "is the most widely used in the treatment of HRS." *Id.* at 241–42. Specifically, "[t]erlipressin has been used in more than 300 patients either as i.v. bolus moving from an initial dose of 0.5 mg every 4 – 6 h[ours], or as a continuous intravenous infusion moving from an initial dose of 2 mg/day." *Id.* at 242. Angeli explains that a patient's response to terlipressin is measured by the patient's reduction of serum creatinine (SCr). *Id.* According to Angeli, "[t]he rate of response, defined with a decrease of SCr > 50% in patients with type 1 HRS, commonly ranges between 40% and 50%." *Id.*

3. Fimiani

Fimiani provides a study of "[t]he use of terlipressin in cirrhotic patients with refractory ascites and normal renal function." Ex. 1006, 587 (Abstract). According to Fimiani, "[t]his prospective study was aimed at evaluating whether terlipressin in addition to standard therapy (diuretics plus albumin) might improve the outcome of refractory ascites in cirrhotic patients without HRS." *Id.* at 588. Cirrhotic patients with refractory ascites received standard diuretic therapy and albumin, followed by a bolus

injection of terlipressin at 0.5 mg every 6 hours. *Id.* Three parameters were measured in response to terlipressin: severity of ascites, body weight, and urinary sodium excretion; "[i]mprovement of all the three parameters plus reduction of abdominal circumference of at least 10% was defined as complete response." *Id.* Fimiani reports that terlipressin improved the outcome of refractory ascites in patients without HRS and reduced ascetic fluid in the abdominal cavity. *Id.* at 589. According to Fimiani, "[o]ur data clearly show that the combined treatment with terlipressin plus diuretics and albumin might improve the outcome of refractory ascites in patients without HRS, decreasing the need for large paracentesis, increasing urinary sodium excretion and reducing abdominal circumference as well as ascites severity." *Id.*

E. Anticipation by Robertson

Petitioner contends that Robertson anticipates claims 1–3 and 5 of the '945 patent because Robertson "expressly discloses each and every element of claims 1–3 and 5." Pet. 20. Specifically, Petitioner contends that "Robertson discloses administering terlipressin to a 59-year-old man with Child-Pugh C cirrhosis due to previous alcohol consumption complicated by diuretic-resistant ascites." *Id.* at 21 (citing Ex. 1004, 2125; Ex. 1002 ¶ 74). Petitioner contends that an ordinarily skilled artisan would understand that "Child-Pugh C cirrhosis is a form of liver cirrhosis" and, thus, the "diuretic-resistant ascites of the 59-year-old man was due to the patient having liver cirrhosis." *Id.* (citing Ex. 1002 ¶ 75). Petitioner also contends that "Robertson discloses that terlipressin was administered as a continuous infusion, at a dose of 3 mg terlipressin in 50 mL 5% dextrose delivered by a GemStar pump at a rate of 2.1 mL/h, for 5 days as an inpatient and for

22 days as an outpatient (i.e. an ambulatory patient)." *Id.* at 22 (citing Ex. 1004, 2125; Ex. 1002 ¶ 76). Patent Owner opposes. PO Resp. 33–35; PO Sur-reply 5–6.

Having considered the totality of the arguments and evidence, we find that Petitioner has shown, by a preponderance of the evidence, that Robertson anticipates claims 1–3 and 5 of the '945 patent.

1. Claim 1

We find that Robertson teaches explicitly each and every limitation of claim 1. As to the preamble, we agree with Petitioner that Robertson discloses "treating a patient diagnosed with ascites due to liver cirrhosis," as interpreted above. *Supra* § III.C.1. Robertson teaches administering terlipressin to a patient having "Child-Pugh C cirrhosis due to previous alcohol consumption complicated by recurrent encephalopathy, diuretic-resistant ascites, and hepatocellular carcinoma." Ex. 1004, 2125. We credit and rely on Dr. Gow's unrebutted testimony that "Child-Pugh C cirrhosis is a form of liver cirrhosis" and, therefore, an ordinarily skilled artisan would understand that the 59-year-old man's ascites was due to liver cirrhosis. Ex. 1002 ¶ 75. We also note that Patent Owner admits that Robertson's patient was diagnosed with ascites due to cirrhosis and that "terlipressin was used to treat the patient's HRS." *See* PO Resp. 34 (citing Ex. 1004, 2125). Robertson also discloses that the patient's serum creatinine concentration was reduced, thus indicating an improvement in renal function. Ex. 1004, 2125–2126; *see also* Ex. 1001, 1:60–67, 3:40–46, 7:20–40 (all identifying "a reduction in serum creatinine concentration" as an indicator for improved renal function). Accordingly, Robertson discloses "treating a patient diagnosed with ascites due to liver cirrhosis," as claimed.

Turning to the remaining limitation of claim 1, we agree with Petitioner that Robertson discloses "administering terlipressin or salt thereof as a continuous infusion dose of about 1.0 mg to about 12.0 mg per day to the patient for about one day to about 12 months." *See* Pet. 22–23. Robertson discloses that the patient was administered a terlipressin infusion "consisting of 3 mg terlipressin in 50 mL 5% dextrose delivered by a GemStar pump at a rate of 2.1 mL/h." Ex. 1004, 2125. Again, we credit and rely on Dr. Gow's unrebutted testimony that a dose of 3 mg terlipressin in 50 mL dextrose at a rate of 2.1 mL/h equals a dosage of 3.024 mg terlipressin a day, which falls within the range recited in claim 1. Ex. 1002 ¶ 77; *see also* Ex. 1001, 2:50–59 (citing Robertson for successfully treating HRS-1 patients with 3 mg/day terlipressin). Robertson also discloses that the terlipressin infusion continued for 5 days as an inpatient and for 22 days as an outpatient, "at which time the patient underwent successful liver transplantation." Ex. 1004, 2125. We find that this time period—27 days—falls within the range recited in claim 1. *See* Ex. 1002 ¶ 79.

Patent Owner's arguments that Robertson fails to anticipate are not persuasive. *See* PO Resp. 33–35; PO Sur-reply 5–6. In this regard, Patent Owner's arguments depend on its interpretation of the preamble as requiring treatment of a patient *for* ascites. *See* PO Resp. 33–35 (stating that "Robertson is silent regarding any effect of the terlipressin treatment (bolus or continuous infusion) on the patient's ascites and never suggests the potential use of terlipressin (alone or with albumin) as a treatment of ascites"); *id.* at 35 (stating that "[t]here is nothing in Robertson that demonstrates, or that would have led [an ordinarily skilled artisan] to conclude, that the terlipressin administered to the patient in Robertson

treated the patient's ascites"); *id.* (arguing that, "[u]nder the broadest reasonable construction, claim 1 is directed to the administration of the continuous terlipressin infusion to treat the patient's ascites"); PO Sur-reply 6 (arguing that Robertson does not anticipate "when the claims are properly construed").

Even though we agree with Patent Owner that Robertson does not expressly teach treating ascites, Petitioner does not allege that Robertson does so. *See* Ex. 2039, 74:11–24 (testimony of Dr. Gow that Robertson is "not reporting to treat ascites with terlipressin"); Tr. 21:11–17 (Petitioner's counsel acknowledging that "[i]f the claim is limited to treating patients for the ascites, Robertson does not disclose that"). Instead, Petitioner contends—and we agree—that Robertson teaches administering terlipressin to a patient diagnosed with ascites to treat the patient's HRS, which falls within the scope of claim 1. Ex. 1004, 2125. As explained above, the plain language of claim 1 encompasses a method for treating a patient *diagnosed with* ascites due to liver cirrhosis for any reason—including for treating a patient's HRS as Robertson teaches—and is not limited to the treatment of ascites itself. *Supra* § III.C.1. For these reasons, Petitioner has shown by a preponderance of the evidence that Robertson anticipates claim 1.

2. Claim 2

Claim 2 depends from claim 1 and recites "wherein the continuous terlipressin is administered for about one day to about six months." Ex. 1001, 8:30–31. Petitioner argues that Robertson discloses this limitation for the same reason that Robertson discloses administering terlipressin "for about one day to about 12 months" in claim 1. Pet. 23–24. Patent Owner

does not raise additional arguments specific to dependent claim 2. *See generally* PO Resp. 33–37; PO Sur-reply 5–6.

As explained above, Robertson discloses that the terlipressin infusion continued for 5 days as an inpatient and for 22 days as an outpatient, "at which time the patient underwent successful liver transplantation." Ex. 1004, 2125. This time period—27 days—falls within the range recited in claim 2. *See* Ex. 1002 ¶¶ 83–85. Thus, Petitioner has shown by a preponderance of the evidence that Robertson anticipates claim 2.

3. Claim 3

Claim 3 depends from claim 1 and recites "wherein the continuous terlipressin is administered with an ambulatory infusion pump." Ex. 1001, 8:33–34. Petitioner argues that Robertson discloses this limitation. Pet. 24. Patent Owner does not raise additional arguments specific to dependent claim 3. *See generally* PO Resp. 33–37; PO Sur-reply 5–6.

As explained above, Robertson discloses that the patient was administered a terlipressin infusion "consisting of 3 mg terlipressin in 50 mL 5% dextrose delivered by a GemStar pump at a rate of 2.1 mL/h." Ex. 1004, 2125. We credit and rely on Dr. Gow's unrebutted testimony that a GemStar pump is a type of ambulatory infusion pump. Ex. 1002 ¶ 87. Thus, Petitioner has shown by a preponderance of the evidence that Robertson anticipates claim 3.

4. Claim 5

Claim 5 depends from claim 1 and recites "wherein the administration of terlipressin is provided on an out-patient basis." Ex. 1001, 8:37–38. Petitioner argues that Robertson discloses this limitation. Pet. 24; *see also* Ex. 1002 ¶¶ 89–90 (Dr. Gow's testimony that Robertson discloses

administering terlipressin on an out-patient basis). Patent Owner does not raise additional arguments specific to dependent claim 5. *See generally* PO Resp. 33–37; PO Sur-reply 5–6.

As explained above, Robertson discloses that the terlipressin infusion continued for 5 days as an inpatient and for 22 days as an outpatient. Ex. 1004, 2125. Because Robertson teaches the administration of terlipressin on an out-patient basis, Petitioner has shown by a preponderance of the evidence that Robertson anticipates claim 5.

F. Obviousness over Fimiani and Robertson or Angeli

Petitioner contends that claims 1–14 are unpatentable as having been obvious over Fimiani in view of Robertson or Angeli. Pet. 35–65. Patent Owner opposes. PO Resp. 48–61; PO Sur-reply 6–23. Having considered the totality of the arguments and evidence, we find that Petitioner has shown by a preponderance of the evidence that claims 1–14 are unpatentable as having been obvious over Fimiani and Robertson or Angeli.

1. Limitations of the challenged claims

Petitioner contends that the combination of Fimiani with Robertson or Angeli discloses or suggests each element of the challenged claims. Petitioner presents arguments mapping the language of claims 1–14 to the disclosures of each reference. Pet. 37–65. We have reviewed Petitioner's arguments and, for the reasons articulated below, find that a preponderance of the evidence supports Petitioner's contentions.

a) Claim 1

The preamble of claim 1 recites "[a] method for treating a patient diagnosed with ascites due to liver cirrhosis." Ex. 1001, 8:25–26. As explained above, we interpret the preamble to encompass treating a patient

diagnosed with ascites due to liver cirrhosis for any reason, not limited to the treatment of ascites itself. *Supra* § III.C.1.

Fimiani discloses the treatment of 26 cirrhotic patients with refractory ascites without HRS. Ex. 1006, 587 (Abstract). Of those patients, 16 had "HCV-related cirrhosis," 2 had "HBV-related" cirrhosis, and 7 had "alcohol cirrhosis." *Id.* at 588. "[A]ll the patients had tense (grade 3) ascites." *Id.* We credit and rely on Dr. Gow's unrebutted testimony that the ordinarily skilled artisan would have understood that "the refractory ascites of the 'cirrhotic patients' was due to the patients having liver cirrhosis." Ex. 1002 ¶ 146. Fimiani found that adding terlipressin to the standard treatment (i.e., albumin and diuretics) caused an increase in urinary sodium excretion and a reduction in abdominal circumference, as well as a reduction in ascites severity, in those patients. Ex. 1006, 589. Accordingly, Fimiani discloses "treating a patient diagnosed with ascites due to liver cirrhosis," as claimed. And, for reasons discussed above, Robertson also teaches this limitation of claim 1. *Supra* § III.E.1.

The remaining limitation of claim 1 recites "the method comprising administering terlipressin or salt thereof as a continuous infusion dose of about 1.0 mg to about 12.0 mg per day to the patient for about one day to about 12 months." Ex. 1001, 8:26–29. Fimiani discloses treating patients with a bolus administration of terlipressin of 0.5 mg every 6 hours (i.e., 2 mg/day), with a progressive increase up to 1 mg qid[7] (i.e., 4 mg/day) for

[7] Dr. Gow explains that an ordinarily skilled artisan would have understood that "qid" is a term of art meaning "four times daily." Ex. 1002 ¶ 152. Thus, "up to 1 mg qid" means "up to 1 mg four times daily" or 4 mg/day. *Id.*

three weeks. Ex. 1006, 588; Ex. 1002 ¶¶ 151–152. Thus, Fimiani discloses administering terlipressin to patients diagnosed with ascites due to liver cirrhosis at both a dosage (2 mg to 4 mg per day) that falls within the range recited in claim 1 (about 1.0 mg to about 12.0 mg per day), and a time period (three weeks) that falls within the range recited in claim 1 (about one day to about 12 months). *See e.g.*, *In re Wertheim*, 541 F.2d 257, 267 (CCPA 1976) (where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a *prima facie* case of obviousness exists). Fimiani, however, does not disclose the route of administration—i.e., "continuous infusion." Pet. 38–39.

Robertson teaches continuous terlipressin administration as an alternative to bolus administration "with similar efficacy and often using a lower total dose, representing a potential cost saving." Ex. 1004, 2125. And, for reasons discussed above, Robertson also teaches administering terlipressin at a dosage and time period falling within the claimed ranges. *Supra* § III.E.1; *see also* Pet. 40. Angeli teaches "continuous intravenous infusion" of terlipressin, at an initial dose of 2 mg/day to a maximum dose of 12 mg/day, with the length of treatment usually between 10 to 15 days. Ex. 1005, 242. Thus, Angeli teaches administering terlipressin at a dosage and time period falling within the claimed ranges. Pet. 54–55.

Patent Owner argues that Fimiani does not teach or suggest that terlipressin treats (i.e., improves) ascites or reduces the accumulation of ascitic fluid in the abdominal cavity in an ambulatory ascites patient. *See* PO Resp. 49–53. Specifically, Patent Owner argues that the claims require that "the improvement [in a patient's ascites] must be caused by the terlipressin (or a salt thereof)." PO Resp. 49. At the outset, we reiterate that

the preamble of claim 1 encompasses the treatment of a patient diagnosed with ascites due to liver cirrhosis for any reason, and is not limited to the treatment of ascites itself. *Supra* § III.C.1. Even so, we find that Fimiani teaches treating (i.e., improving) a patient's ascites.

Specifically, Fimiani discloses administering terlipressin, albumin, and diuretics to cirrhotic patients with refractory ascites. Ex. 1006, 587 (Abstract). Fimiani found that adding terlipressin to the standard treatment (i.e., albumin and diuretics) caused an increase in urinary sodium excretion and a reduction in abdominal circumference, as well as a reduction in ascites severity, in those patients. *Id.* at 589.

Patent Owner argues that Fimiani does not teach improving ascites or reducing ascitic fluid with *terlipressin* because (1) Fimiani used a combination treatment (i.e., terlipressin, albumin, and diuretics), and thus, could not have concluded that *terlipressin* improved the outcome of ascites in cirrhotic patients, and (2) Fimiani did not use "the controls needed to conclude that terlipressin alone was the cause of the observed effects." PO Resp. 49–50.

Patent Owner's first argument is not persuasive because the claims recite "*comprising* administering terlipressin or a salt thereof." Ex. 1001, 8:26–27 (emphasis added); *see also id.* at 8:44 ("comprising administering to the patient terlipressin or a salt thereof"). The recitation of the term "comprising" does not exclude the administration of the other agents used in Fimiani's treatment regimen—i.e., diuretics and albumin. *See, e.g.*, *Georgia–Pacific Corp. v. United States Gypsum Co.*, 195 F.3d 1322, 1327–28 (Fed. Cir. 1999) (stating that the transitional term "comprising" "is

inclusive or open-ended and does not exclude additional, unrecited elements or method steps").

To the extent Patent Owner implies that terlipressin may have produced *no* effect in Fimiani's patients, we disagree. Fimiani expressly states that the observed improvements in ascites patients (i.e., increase in urinary sodium excretion and reduction in abdominal circumference as well as ascites severity) results from the "synergistic effect *of terlipressin* when added to albumin and diuretics in patients with refractory ascites." Ex. 1006, 589 (emphasis added). Specifically, Fimiani states that standard treatment in patients with refractory ascites consists of albumin plus diuretics. *See id.* at 587 (Abstract). Fimiani notes that "[t]he use of terlipressin in cirrhotic patients with refractory ascites and normal renal function has not been evaluated." *Id.* Thus, Fimiani's "study was aimed at evaluating whether terlipressin in addition to standard therapy (diuretics plus albumin) might improve the outcome of refractory ascites in cirrhotic patients without HRS." *Id.* Fimiani found that adding terlipressin to the standard treatment caused an increase in urinary sodium excretion and a reduction in abdominal circumference, as well as a reduction in ascites severity. *Id.* at 589. Fimiani states that the study "shows a synergistic effect of terlipressin when added to albumin and diuretics in patients with refractory ascites." *Id.*; *see also id.* at 587 (Abstract) ("In conclusion, our study shows a synergistic effect of terlipressin [versus] treatment with albumin plus diuretics in patients with refractory ascites.").

As Dr. Bosch acknowledged during his deposition, an ordinarily skilled artisan would have understood that "[t]he word 'synergistic' implies that you have a greater effect by a combination of therapies in that case than

by any single therapy separately." Ex. 1016, 95:12–19.[8] Thus, an ordinarily skilled artisan would have understood that Fimiani shows that terlipressin had an effect on ascites patients by causing a synergistic effect; that is, terlipressin, along with albumin and diuretics, treated ascites. Given Fimiani's teachings and Dr. Bosch's admission, we find that Fimiani teaches the administration of terlipressin for treating a patient diagnosed with ascites—including for the treatment and improvement of ascites itself as well as for a reduction in ascitic fluid in the abdominal cavity.

As to Patent Owner's second argument, we note that nothing in claim 1 requires "terlipressin alone" to treat the patient. Put differently, and as explained above, the claim—through its use of the term "comprising"—encompasses the administration of terlipressin, albumin, and diuretics as a treatment for ascites patients, which Fimiani teaches. Patent Owner acknowledges that "Fimiani reports that the observed outcomes were the result of the combination of agents used in the study." PO Resp. 49. And Dr. Bosch confirms that "it was the drug combination, rather than terlipressin alone, that was responsible for the effect observed in Fimiani." Ex. 2023 ¶ 106.

In any event, we are not persuaded that Fimiani lacked sufficient controls as to render its teachings about terlipressin irrelevant to an ordinarily skilled artisan. At bottom, Patent Owner's argument is that the

[8] We find that Dr. Bosch's statement about synergism accords with the general knowledge in the art. The Federal Circuit has explained that a "'synergistic' effect" occurs "when the combination's effect exceeds the sum of the separately administered effects." *Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 719 F.3d 1346, 1349 n.2 (Fed. Cir. 2013).

skilled artisan would have disregarded Fimiani's teachings because "Fimiani [is] an example of a poorly conducted study reported by a creative group of authors." PO Sur-reply 7; *see also id.* at 7–8 (criticizing Fimiani's study design). "Because Fimiani lacked a useful control," Patent Owner argues, "no conclusions regarding the impact of terlipressin on the patients' ascites can be drawn from the results." *Id.* at 8 (citing Ex. 2023 ¶¶ 104–105).

We recognize that Fimiani states that "[n]o comparative group was included in this analysis, as the pretreatment period was considered as internal control group." Ex. 1006, 588; *see also* Ex. 2023 ¶ 103 ("That means there were no comparison groups of patients that received, for example, diuretics and albumin but not terlipressin, terlipressin alone, or any other combination of the drugs in the treatment regimen."). But Patent Owner's arguments that Fimiani does not teach or suggest the use of terlipressin to treat ascites and reduce ascitic fluid in ascites patients because of purported study design flaws represents an overly narrow view of the prior art. *See* Pet. Reply 11. We must consider Fimiani "for all that it teaches." *Smith & Nephew, Inc. v. Rea*, 721 F.3d 1371, 1378 (Fed. Cir. 2013). And here, Fimiani clearly teaches "a synergistic effect of terlipressin when added to albumin and diuretics in patients with refractory ascites." Ex. 1006, 589 (Abstract).

The parties debate extensively whether an ordinarily skilled artisan would have considered Fimiani's pretreatment period as a sufficient "internal control group." PO Resp. 50–51; Pet. Reply 12–14; PO Sur-reply 8–12. In our view, however, these considerations are not as relevant to the obviousness analysis here. This is because—at the very least—Fimiani suggests combining terlipressin treatment with standard therapy (diuretics

plus albumin) to "improve the outcome of refractory ascites in cirrhotic patients without HRS." Ex. 1006, 588. Indeed, Fimiani states that the reported "study shows a synergistic effect of terlipressin when added to albumin and diuretics in patients with refractory ascites," and *expressly encourages* skilled artisans to undertake further "prospective, randomized controlled studies . . . to confirm our preliminary data." *Id.* at 589. This disclosure is a sufficient teaching or suggestion of treating a patient with terlipressin as claimed, which is all the law requires. *See, e.g.*, *Beckson Marine, Inc. v. NFM, Inc.*, 292 F.3d 718, 727 (Fed. Cir. 2002) ("[O]bviousness does not require the prior art to reach expressly each limitation exactly. Rather, obviousness may render a claimed invention invalid where the record contains a suggestion or motivation to modify the prior art teaching to obtain the claimed invention."); s*ee also Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014) ("Conclusive proof of efficacy is not necessary to show obviousness.").

For these reasons, we agree with Petitioner that the combination of Fimiani and Robertson or Angeli teaches or suggests each and every limitation of claim 1. *See* Pet. 37–41, 53–55.

b) Dependent claims 2–6, 12, and 13

Having decided that the combination of Fimiani and Robertson or Angeli teaches or suggests each and every limitation of claim 1, we turn to the claims dependent either directly or indirectly on claim 1 (i.e., claims 2–6, 12, and 13). We find that Petitioner also shows by a preponderance of the evidence that Fimiani and Robertson or Angeli account for the limitations in these claims. Pet. 41–44, 49–50. We have also reviewed Dr. Gow's testimony and find that a preponderance of the evidence supports his

contention that the cited references collectively disclose or suggest each and every limitation of claims 2–6, 12, and 13. *See* Ex. 1002 ¶¶ 170–172, 239–240 (claim 2) (citing Ex. 1004, 2125; Ex. 1005, 242; Ex. 1006, 588); *id.* ¶¶ 173–175, 241–245 (claim 3) (citing Ex. 1004, 2125; Ex. 1007); *id.* ¶¶ 176–178, 246–248 (claim 4) (citing Ex. 1006, 588; Ex. 1005, 241, 245); *id.* ¶¶ 179–182, 249–251 (claim 5) (citing Ex. 1004, 2125; Ex. 1007); *id.* ¶¶ 183–187, 252–256 (claim 6) (citing Ex. 1006, 588; Ex. 1005, 242); *id.* ¶¶ 202–205, 270–273 (claim 12) (citing Ex. 1006, 588; Ex. 1005, 241, 245); *id.* ¶¶ 206–208, 274–277 (claim 13) (citing Ex. 1004, 2125; Ex. 1007). Patent Owner does not present separate arguments for any of the dependent claims. *See generally* PO Resp. 48–61. We, therefore, adopt the teachings set forth in the Petition and in Dr. Gow's Declaration as mapped to the limitations of the challenged claims as our own findings. *See In re NuVasive, Inc.*, 841 F.3d 966, 974 (Fed. Cir. 2016) (explaining that the Board need not make specific findings about claim limitations that a patent owner does not dispute are disclosed in the prior art).

c) Claim 7

The preamble of claim 7 recites "[a] method for reducing the accumulation of ascitic fluid in the abdominal cavity in an ambulatory ascites patient." Ex. 1001, 8:42–43. Fimiani reports a reduction of peripheral fluid accumulation as measured by a decrease in body weight, as well as a reduction in the severity of ascites in sixteen of 26 patients. Ex. 1006, 588–89. Although Fimiani does not teach "an *ambulatory* ascites patient," Robertson discloses that terlipressin was administered to an ascites patient for 5 days as an inpatient and for 22 days as an outpatient. Ex. 1004, 2125. Specifically, Robertson describes the patient as "initially receiv[ing] a

terlipressin infusion as an inpatient," but that, "[o]n day 6[,] the patient was discharged home with an ambulatory terlipressin infusion under the supervision of our Hospital-in-the-home program." Ex. 1004, 2125. The parties agree that an "ambulatory ascites patient" is "a non-hospitalized patient" who has "ascites due to any etiology." Pet. 12–13; PO Resp. 14.[9] Thus, we agree with Petitioner that an ordinarily skilled artisan would have understood that Robertson teaches an "ambulatory ascites patient." Pet. 45.

The remaining limitation of claim 7 is substantially identical to that in claim 1, except that claim 7 recites that the administration of terlipressin is with "an ambulatory infusion pump." *Compare* Ex. 1001, 8:27–29 (claim 1) ("the method comprising administering terlipressin or salt thereof as a continuous infusion dose of about 1.0 mg to about 12.0 mg per day to the patient for about one day to about 12 months"), *with id.* at 8:43–47 (claim 7) ("the method comprising administering to the patient terlipressin or salt thereof as a continuous infusion dose of about 1.0 mg to about 12.0 mg per day for about one day to about twelve months with an ambulatory infusion pump").

We reiterate that Fimiani discloses a dosage (2 mg to 4 mg per day) that falls within the range recited in claim7 (about 1.0 mg to about 12.0 mg per day), and a time period (three weeks) that falls within the range recited in claim 7 (about one day to about 12 months). *Supra* § III.F.1.a; *see also* Ex. 1006, 588; Pet. 46–48; Ex. 1002 ¶¶ 151–152. Fimiani, however, does not disclose either the route of administration, i.e., "continuous infusion," or "an ambulatory infusion pump."

[9] This interpretation comports with that in the '945 patent, which equates the term "non-hospitalized" with "ambulatory." Ex. 1001, 2:42–43.

Robertson teaches continuous terlipressin administration as an alternative to bolus administration "with similar efficacy and often using a lower total dose, representing a potential cost saving." Ex. 1004, 2125. Angeli teaches "continuous intravenous infusion" of terlipressin, at an initial dose of 2 mg/day to a maximum dose of 12 mg/day, with the length of treatment usually between 10 to 15 days. Ex. 1005, 242. Robertson also teaches administering a terlipressin infusion "consisting of 3 mg terlipressin in 50 mL 5% dextrose delivered by a GemStar pump at a rate of 2.1 mL/h." Ex. 1004, 2125. Again, we credit and rely on Dr. Gow's unrebutted testimony that a GemStar pump is a type of ambulatory infusion pump. Ex. 1002 ¶ 87. We also credit and rely on Dr. Gow's unrebutted testimony that it was well known in the art that ambulatory infusion pumps were "used to deliver continuous infusions, such as those described in Angeli, to a patient." *Id.* ¶ 228. Other record evidence supports Dr. Gow's testimony that "the use of terlipressin as an outpatient infusion drug was generally known in the art." *Id.* ¶ 230; *see* Ex. 1007 (PharmaIN press release).

Patent Owner's argument in response is the same that it presents with respect to claim 1—i.e., Fimiani does not teach treating (i.e., improving) ascites or reducing the accumulation of ascitic fluid in the abdominal cavity in an ambulatory ascites patient with terlipressin. PO Resp. 49–53. We find these arguments unpersuasive for the reasons explained in connection with claim 1, above. *Supra* § III.F.1.a.

For these reasons, we agree with Petitioner that the combination of Fimiani and Robertson or Angeli teaches or suggests each and every limitation of claim 7. *See* Pet. 44–46, 59–60.

d) Dependent claims 8–11 and 14

We turn now to the claims dependent on claim 7 (i.e., claims 8–11 and 14), and find that Petitioner also shows by a preponderance of the evidence that Fimiani and Robertson or Angeli account for the limitations in these dependent claims. Pet. 48–49, 51, 62–63, 65. We have also reviewed Dr. Gow's testimony and find that a preponderance of the evidence supports his contention that the cited references collectively disclose or suggest each and every limitation of claims 8–11 and 14. *See* Ex. 1002 ¶¶ 188–190, 257–258 (claim 8) (citing Ex. 1004, 2125; Ex. 1005, 242; Ex. 1006, 588); *id.* ¶¶ 191–193, 259–261 (claim 9) (citing Ex. 1006, 588; Ex. 1005, 241, 245); *id.* ¶¶ 194–197, 262–264 (claim 10) (citing Ex. 1004, 2125; Ex. 1007); *id.* ¶¶ 198–201, 265–269 (claim 11) (citing Ex. 1006, 588; Ex. 1005, 242); *id.* ¶¶ 209–212, 278–281 (claim 14) (citing Ex. 1006, 588; Ex. 1005, 241, 245). Patent Owner does not present separate arguments for any of the dependent claims. *See generally* PO Resp. 48–61. We, therefore, adopt the teachings set forth in the Petition and in Dr. Gow's Declaration as mapped to the limitations of the challenged claims as our own findings. *See NuVasive*, 841 F.3d at 974.

2. Motivation to combine/reasonable expectation of success

Even "[i]f all elements of the claims are found in a combination of prior art references," "the factfinder should further consider whether a person of ordinary skill in the art would [have been] motivated to combine those references, and whether in making that combination, a person of ordinary skill would have [had] a reasonable expectation of success." *Merck & Cie v. Gnosis S.P.A.*, 808 F.3d 829, 833 (Fed. Cir. 2015). The "motivation to combine" and "reasonable expectation of success" factors are

subsidiary requirements for obviousness subsumed within the *Graham* factors. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007). We address motivation to combine and reasonable expectation of success in turn below.

a) Motivation to combine

Petitioner contends, and Dr. Gow testifies, that an ordinarily skilled artisan would have had a reason to combine the teachings of Fimiani with Robertson. Pet. 35–37 (citing Ex. 1002 ¶¶ 150, 158, 159, 164). Specifically, Petitioner contends that an ordinarily skilled artisan, at the time of the '945 patent, "would have been motivated to treat the patient population of Fimiani using the continuous infusion administration route taught by Robertson" because (1) Robertson teaches that "'[m]ultiple case reports now exist describing continuous terlipressin infusion as an alternative to intravenous bolus administration, with similar efficacy and often using a lower total dose, representing a potential cost saving,'" *id.* at 35 (quoting Ex. 1004, 2125), and (2) "Robertson teaches terlipressin administration of 3 mg/day for 22 days as an outpatient, which overlaps with the dosage ranges and durations taught by Fimiani (i.e., 2 to 4 mg/day for three weeks)," *id.* Petitioner also contends that an ordinarily skilled artisan "would have been motivated to treat the patient population studied in the clinical trial of Fimiani on an outpatient basis, as described in Robertson, because the Fimiani subjects did not have renal failure or any other comorbidity that required hospitalization." *Id.* at 36 (citing Ex. 1002 ¶ 159). Petitioner contends that it "would have been apparent to [an ordinarily skilled artisan] that continuous administration freed the patients of Fimiani

from having to receive intravenous boluses every 6 hours, most likely in a hospital setting." *Id.*

Further, Petitioner contends, and Dr. Gow testifies, that an ordinarily skilled artisan would have had a reason to combine the teachings of Fimiani with Angeli. *Id.* at 51–53 (citing Ex. 1002 ¶¶ 216–218). Specifically, Petitioner contends that the ordinarily skilled artisan "would have been motivated to treat the patient population of Fimiani using the continuous infusion administration route taught by Angeli" because (1) "Angeli teaches that 'terlipressin given by continuous intravenous infusion is more effective and better tolerated than when it is given by intravenous boluses,'" *id.* at 51–52 (quoting Ex. 1005, 241), (2) "Angeli teaches terlipressin administration of 2 mg/day to 12 mg/day for 10–15 days which overlaps with the dosage ranges and durations taught by Fimiani," *id.* at 52, and (3) "Angeli teaches the benefit of early administration of terlipressin to patients suffering from cirrhosis and ascites, at least prior to progression to HRS type 1," *id.* Petitioner also contends that an ordinarily skilled artisan "would have been motivated to modify the route of administration taught by Fimiani (IV bolus) as taught by Angeli (continuous infusion) because it was general knowledge in the art that ascites develops when there is severe portal hypertension and Angeli teaches that continuous infusion will maximize the effectiveness of terlipressin on portal pressure." *Id.* at 52–53 (citing Ex. 1006, 587; Ex. 1002 ¶ 217).

(1) Motivation to substitute continuous infusion administration for bolus administration

Upon review of the complete record, we find that Petitioner has shown, by a preponderance of the evidence, that an ordinarily skilled artisan

would have been motivated to combine the teachings of Fimiani and Robertson or Angeli; that is, to substitute the bolus method of terlipressin administration in Fimiani with the continuous infusion method of terlipressin administration in Robertson or Angeli. Pet. 35–36, 52–53.

To begin, we note that Fimiani expressly encourages skilled artisans to undertake further "prospective, randomized controlled studies . . . to confirm [its] preliminary data" that terlipressin, when added to the albumin and diuretics standard therapy in patients with refractory ascites, produces a synergistic effect. Ex. 1006, 589. We agree with Petitioner than an ordinarily skilled artisan undertaking those experiments—and looking to improve administration of terlipressin to ascites patients—would have had a reason to look to Robertson or Angeli.

Robertson expressly suggests using continuous terlipressin infusion as a replacement for bolus administration (as Fimiani teaches) to reduce costs. Ex. 1004, 2125. Robertson also expressly suggests administering continuous terlipressin infusion on an outpatient basis (i.e., an ambulatory or non-hospitalized patient), as recited in claim 7. *Id.* Indeed, Robertson explains that "[m]ultiple case reports now exist describing continuous terlipressin infusion as an alternative to intravenous bolus administration, with similar efficacy and often using a lower total dose, representing a potential cost saving." Ex. 1004, 2125. The objective of Robertson's study was to show that, although "[t]erlipressin is traditionally given using a bolus regimen in a hospital setting," the administration of continuous terlipressin in an outpatient setting is not only "feasible," but also "efficacious[] and well tolerated." *Id.* at 2125–26. Thus, Robertson "present[s] the first reported case of an outpatient continuous terlipressin infusion for treatment

of recurrent HRS as a bridge to successful liver transplantation." *Id.* at 2125.

Given Robertson's successful results, we agree with Petitioner that an ordinarily skilled artisan would have been motivated to treat the patient population studied in the Fimiani's clinical trial with continuous terlipressin infusion, as recited in claim 1, and to treat an ambulatory ascites patient (i.e., on an outpatient basis), as recited in claim 7. Pet. 36. As to the latter, we find credible and persuasive Dr. Gow's testimony that, because the Fimiani patients did not have renal failure or any other comorbidity that required hospitalization, "[i]t would have been apparent to [an ordinarily skilled artisan] that continuous administration freed the patients of Fimiani from having to receive intravenous boluses every 6 hours, most likely in a hospital setting." Ex. 1002 ¶ 159.

We also note that Robertson's terlipressin administration (i.e., 3 mg/day for 22 days as an outpatient) overlaps with the dosage ranges and durations that Fimiani teaches (i.e., 2 to 4 mg/day for three weeks). These factors together persuade us that an ordinarily skilled artisan would have been motivated to substitute the bolus method of terlipressin administration in Fimiani with the continuous infusion method of terlipressin administration in Robertson, and, on an outpatient basis. Here, the combination of references provides cost savings in terms of both the amount of terlipressin needed and the length of hospital stays. Ex. 1004, 2125–26; Ex. 1002 ¶ 159. *See DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1368 (Fed. Cir. 2006) (explaining that a "motivation to combine exists not only when a suggestion may be gleaned from the prior art as a whole, but when the 'improvement' is technology-

independent and the combination of references results in a product or process that is more desirable, for example because it is stronger, cheaper, cleaner, faster, lighter, smaller, more durable, or more efficient").

For the same reasons, we also agree with Petitioner that an ordinarily skilled artisan would have had a reason to substitute Fimiani's bolus administration with Angeli's continuous infusion. Pet. 52–53. Angeli states that "terlipressin given by continuous intravenous infusion is more effective and better tolerated than when it is given by intravenous boluses," Ex. 1005, 241, that "the use of terlipressin by continuous intravenous infusion may turn out to be safer and cheaper than that by continuous intravenous boluses," and that terlipressin may be used in "lower dose[s]" when administered "by continuous intravenous infusion rather tha[n] when it is given by intravenous boluses," *id.* at 245. Thus, we find that Angeli provides express motivation to substitute Fimiani's bolus administration with continuous terlipressin infusion, because continuous infusion is more effective, better tolerated, safer, and cheaper. *See* Ex. 1002 ¶ 216. We also note that Angeli, like Robertson, teaches terlipressin administration of 2 mg/day to 12 mg/day for 10–15 days, which overlaps with the dosage ranges and durations that Fimiani teaches, further supporting Petitioner's reason to combine. Pet. 52.

Although we have carefully considered Patent Owner's arguments and evidence in response, we are persuaded that Petitioner has provided sufficient reason with rational underpinning for combining Fimiani with Robertson or Angeli. *KSR*, 550 U.S. at 418. Patent Owner argues that an ordinarily skilled artisan would not have been motivated to pursue continuous terlipressin infusion because terlipressin "had known dangerous

side effects, including serious cardiac and ischemic side effects," PO Resp. 54 (citing Ex. 2023 ¶¶ 110, 111, 135; Ex. 2039, 9:22–25), the art "cautioned against using terlipressin in non-HRS patients, such as the patients in Fimiani, *id.* (citing Ex. 2023 ¶ 135), and "[o]ther . . . literature suggested that terlipressin should not be used on an outpatient basis," *id.* (citing Ex. 2023 ¶¶ 111–114, 135).

Of these three arguments, only the final one is relevant to whether an ordinarily skilled artisan would have had a reason *to combine* Fimiani with Robertson or Angeli—i.e., to substitute Fimiani's bolus administration with Robertson's or Angeli's continuous terlipressin infusion.[10] Patent Owner argues that an ordinarily skilled artisan would not have employed terlipressin on an outpatient basis because "the patient cannot be monitored for the side effects" of terlipressin. PO Resp. 56 (citing Ex. 2023 ¶137). Patent Owner's argument, however, is not persuasive because it lacks credible and specific support in the record. As support for its argument, Patent Owner cites only to paragraph 137 of Dr. Bosch's Declaration. But that paragraph merely repeats, without adequate elaboration or explanation, Patent Owner's argument. Thus, we decline to give weight to this portion of

[10] To be clear, Patent Owner's first two arguments address whether an ordinarily skilled artisan would have had a reason to pursue and use terlipressin in the first place, which we address elsewhere. *Infra* § III.F.2.1. In any event, we agree with Petitioner that Patent Owner's arguments are "difficult to understand" because Fimiani reports that "[d]uring treatment with terlipressin, no significant adverse events were seen." Ex. 1006, 589; *see also* Pet. Reply 17–20. We also note that Patent Owner presents no credible evidence or argument that the side effects of terlipressin would differ depending on the route of administration (i.e., bolus administration or continuous infusion). *See generally* PO Resp. 54–57.

Dr. Bosch's testimony. *See In re Am. Acad. of Sci. Tech Ctr.*, 367 F.3d 1359, 1368 (Fed. Cir. 2004) ("[T]he Board is entitled to weigh the declarations and conclude that the lack of factual corroboration warrants discounting the opinions expressed in the declarations."); *see also* 37 C.F.R. § 42.65(a) ("Expert testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight.").

Moreover, we find credible, and supported with record evidence, Dr. Gow's unrebutted testimony that it was well known in the art that ascites develops when there is severe portal hypertension. Ex. 2002 ¶ 217; *see also* Ex. 1006, 587 (stating that ascites "develops late during the course of [liver cirrhosis], when there are severe portal hypertension and hepatic insufficiency"). Angeli teaches that the use of intravenous boluses to administer terlipressin (which typically occurred every 4 to 6 hours) "does not appear to be the best way of maximizing the effect of terlipressin" because "the effect of terlipressin on portal pressure has been shown to last less than 4 h[ours]." Ex. 1005, 245. Given the relationship between ascites and portal hypertension, we agree with Petitioner that Angeli's teachings would have provided the ordinarily skilled artisan with an additional reason to substitute Fimiani's bolus administration with continuous infusion of terlipressin—i.e., to maximize the effectiveness of terlipressin on portal pressure. Pet. 52–53; Ex. 1006, 587; Ex. 1002 ¶ 217.

(2) Motivation to pursue and use terlipressin

Patent Owner also argues that an ordinarily skilled artisan would not have been motivated to pursue terlipressin for the treatment of ascites or for the reduction of ascitic fluid in the first place. In this regard, Patent Owner essentially repeats the same arguments described above in connection with

Fimiani's teachings of the claim limitations—i.e., that Fimiani "did not attribute the observed effects on renal function and ascites solely to terlipressin," PO Resp. 53, and that an ordinarily skilled artisan could not have concluded from Fimiani that terlipressin improved the outcome of ascites in cirrhotic patients, PO Sur-reply 14. Again, these arguments are not persuasive for the reasons we explain above, including for the reason that the claims do not require the treatment to be attributable "solely to terlipressin." *Supra* § III.F.1.

Next, Patent Owner argues that an ordinarily skilled artisan would have known "that the combination of diuretics and albumin (without terlipressin) had been shown to resolve ascites in patients with liver cirrhosis," and thus, would not have had a reason to attempt to improve that treatment. PO Resp. 53–54. Patent Owner relies on the teachings of Gentilini[11] and Schindler[12] to argue that the ordinarily skilled artisan would not have been motivated to pursue terlipressin treatment because those references (in combination with Fimiani) suggest "that it was the albumin (and diuretics), rather than terlipressin, in Fimiani that was the cause of the effect on ascites." *Id.* at 52–53 (citing Ex. 2023 ¶¶ 132–133).

We do not agree that Gentilini or Schindler, even when considered in combination with Fimiani, would have discouraged the skilled artisan from

[11] Paulo Gentilini et al., *Albumin improves the response to diuretics in patients with cirrhosis and ascites: results of a randomized, controlled trial*, 30 J. HEPATOLOGY 639–45 (1999) ("Gentilini," Ex. 2008).

[12] Christian Schindler and Guiliano Ramadori, *Albumin substitution improves urinary sodium excretion and diuresis in patients with liver cirrhosis and refractory ascites*, 31 J. HEPATOLOGY 1132 (1999) ("Schindler," Ex. 2036).

pursuing terlipressin treatment strategies. Gentilini provides the results of a drug trial "aimed at evaluating whether intravascular volume expansion with human albumin exerts beneficial effects in patients with ascites receiving diuretics." Ex. 2008, 640. Gentilini concluded that "[a]lbumin is effective in improving the rate of response and preventing recurrence of ascites in cirrhotic patients with ascites receiving diuretics." *Id.* at 639. Similarly, Schindler reports that "albumin substitution in addition to diuretic therapy may normalize urinary sodium excretion in patients with refractory ascites and cirrhosis of the liver." Ex. 2036, 1132.

Importantly, however, neither Gentilini nor Schindler mentions terlipressin, *see generally* Ex. 2008; Ex. 2036, and both references were published in 1999, more than a decade before the 2011 Fimiani publication date. Fimiani expressly suggests the desirability of adding terlipressin to the standard therapy of albumin and diuretics described in the prior art (and evidenced here by Gentilini and Schindler), due to terlipressin's "synergistic effect . . . when added to albumin and diuretics in patients with refractory ascites." Ex. 1006, 589. Given Fimiani's express teachings and the substantial length of time between the publication of Gentilini and Schindler and the publication of Fimiani, we find unpersuasive Patent Owner's argument that an ordinarily skilled artisan would have been discouraged from making Fimiani's expressly suggested improvements to the standard therapy of albumin and diuretics.

(3) Summary as to motivation to combine

For all the above reasons, we find that Petitioner has shown, by a preponderance of the evidence, that an ordinarily skilled artisan would have

been motivated to combine the teachings of Fimiani and Robertson or Angeli to achieve the claimed invention.

b) Reasonable expectation of success

We next consider whether Petitioner has shown by a preponderance of the evidence that the skilled artisan would have had a reasonable expectation of success in achieving the method claimed in the '945 patent. "The reasonable expectation of success requirement refers to the likelihood of success in combining references to meet the limitations of the claimed invention." *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016).

As explained above, Fimiani teaches every limitation of claim 1 (e.g., the claimed amount of terlipressin (about 1.0 mg to about 12.0 mg per day) and the claimed duration of treatment (about one day to about 12 months) administered to patients diagnosed with ascites due to liver cirrhosis), except for the route of administration, i.e., "continuous infusion." *Supra* § III.F.1.a. And, as to claim 7, Fimiani also fails to teach "an ambulatory ascites patient." *Id.* § III.F.1.c. The relevant question before us, therefore, is whether the ordinarily skilled artisan would have had a reasonable expectation that using Robertson's or Angeli's continuous infusion administration would have been successful in treating a patient diagnosed with ascites due to liver cirrhosis (as recited in claim 1), and in reducing the accumulation of ascitic fluid in the abdominal cavity in an ambulatory ascites patient (as recited in claim 7).

Upon consideration of the entire record, we find that the preponderance of the evidence answers those questions in the affirmative. In making our findings as to "reasonable expectation of success," we keep in

mind that we cannot demand absolute certainty. *See Intelligent Bio-Sys.*, 821 F.3d at 1367 ("While the definition of 'reasonable expectation' is somewhat vague, our case law makes clear that it does not require a certainty of success."); *see also Pfizer*, 480 F.3d at 1364 ("[C]ase law is clear that obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success.").

Here, we agree with Petitioner that an ordinarily skilled artisan would have reasonably expected continuous infusion of terlipressin to be successful, because both Fimiani and each of Robertson and Angeli use overlapping doses of terlipressin and both report improved renal function in their respective patient populations. Pet. 36, 55; Ex. 1002 ¶¶ 158, 224. We also agree with Petitioner that the skilled artisan would have expected "that patients could be successfully treated on an outpatient basis with terlipressin." Pet. 36; Ex. 1002 ¶ 164. In this regard, Dr. Gow testifies—and we agree—that Robertson evinces an improvement in renal function in patients with ascites from continuous doses of 3 mg/day, as well as the feasibility of outpatient treatment. Ex. 1002 ¶ 150. As to the latter, Dr. Gow points out that Robertson successfully treated an HRS type 1 patient awaiting transplant—"a patient far more critically ill than those of Fimiani that did not have HRS"—for 22 days as an outpatient. *Id.*

We discern no specific or credible argument from Patent Owner as to reasonable expectation of success of substituting continuous infusion administration for bolus administration. Patent Owner's argument appears to be that there would have been no reasonable expectation of success in treating ascites (or reducing ascitic fluid) with terlipressin, regardless of

whether administration of terlipressin is by bolus injection or continuous infusion. *See* PO Resp. 57–58; PO Sur-reply 20–23. In its Sur-reply, however, Patent Owner asserts for the first time that an ordinarily skilled artisan would not have had a reasonable expectation of success given "differences in the pharmacokinetic (PK) profile of the plasma concentrations associated with bolus and continuous infusion terlipressin dosing." PO Sur-reply 20 (citing Ex. 2044 ¶ 6). But we do not take that testimony into account because we grant-in-part Petitioner's motion to strike citations to Exhibit 2044 in the Sur-reply. *See supra* § II. Thus, no specific and persuasive evidence supports Patent Owner's arguments.

As noted in the procedural history, after the oral hearing in this case Patent Owner filed a Notice of Supplemental Authority directed to the Federal Circuit's decision in *OSI Pharms., LLC v. Apotex Inc.*, 939 F.3d 1375 (Fed. Cir. 2019). And Petitioner filed a Reply. In *OSI Pharmaceuticals*, the Federal Circuit reversed the Board's determination that certain claims to methods for treating non-small cell lung cancer (NSCLC) with the drug erlotinib were unpatentable as having been obvious, concluding that substantial evidence did not support the Board's finding of reasonable expectation of success. 939 F.3d at 1377.

In its analysis below, the Board first found that the prior-art reference Gibbs provided "a clear inference" that "erlotinib has anti-cancer activity against non-small cell lung cancer." *Id.* at 1383. The Board then found that the combination of Gibbs with prior-art reference Schnur, or Schnur with OSI's Form 10-K, "would have provided a person of ordinary skill with a reasonable expectation of success in using erlotinib to treat NSCLC in a mammal." *Id.* at 1384.

On review, the Federal Circuit found as an initial matter that the Board "misinterpreted the asserted references to teach more than substantial evidence supports." *Id.* at 1377–78. With respect to Gibbs, the Court noted that Gibbs "is a review article that collects, reviews, and analyzes other research studies." *Id.* at 1383. And looking to the underlying references cited in Gibbs, the Court found that none of those references discusses erlotinib's effect on NSCLC. *Id.* at 1383–84. The Court then turned to reasonable expectation of success, and found that, once properly read, the asserted combinations of prior art "do not provide substantial evidence supporting the Board's findings of reasonable expectation of success." *Id.* at 1384.

The Court noted that Schnur "fails to disclose any *in vitro* or *in vivo* efficacy data for erlotinib or otherwise suggest the use of erlotinib to treat NSCLC." *Id.* The combination of Gibbs and Schnur, the Court explained, thus at most taught only that erlotinib "has good anticancer activity in some cancers, *not* including NSCLC." *Id.* The Court found "significant" the lack of efficacy data "or other indication of success" because of (1) the "highly unpredictable nature of treating NSCLC, which is illustrated by the over 99.5% failure rate of drugs entering Phase II," and (2) the undisputed fact "that a drug's success in treating one type of cancer does not necessarily translate to success in treating a different type of cancer." *Id.* Similarly, as to the combination of Schnur and OSI's 10-K, the Court found "[n]otably absent from this combination . . . any data or other information regarding erlotinib's effect on NSCLC." *Id.* at 1385.

Given these facts, the Court concluded that:

> These references provide no more than hope—and hope that a potentially promising drug will treat a particular cancer is not enough to create a reasonable expectation of success in a highly unpredictable art such as this. Indeed, given a 99.5% failure rate and no efficacy data or any other reliable indicator of success, the only reasonable expectation at the time of the invention was failure, not success. It is only with the benefit of hindsight that a person of skill in the art would have had a reasonable expectation of success in view of the asserted references.

Id.

In its Notice, Patent Owner argues that the facts of this case are like those presented in *OSI Pharmaceuticals*. PO Notice 1. Specifically, Patent Owner argues that, "like the asserted references in *OSI Pharmaceuticals*, the asserted references in the present proceeding do not disclose information or reliable data about terlipressin's efficacy in treating ascites." *Id.* at 2. Thus, Patent Owner argues, those references "would not have provided a person of ordinary skill in the art with a reasonable expectation of success that continuous infusion terlipressin would treat ascites in patients." *Id.* Petitioner responds that *OSI Pharmaceuticals* "was decided on facts not present in this proceeding and thus irrelevant to the Board's final determination in this matter." Pet. Reply to Notice 1.

Upon review of the Federal Circuit's decision and the parties' respective arguments, we find that Petitioner has the better position. Unlike in *OSI Pharmaceuticals*, the record in this case does contain information that terlipressin can be used successfully treat patients diagnosed with ascites and reduce the accumulation of ascitic fluid. Specifically, Fimiani reports that the addition of terlipressin to standard treatment (albumin and diuretics) caused an increase in urinary sodium excretion and a reduction in abdominal

circumference as well as ascites severity. Ex. 1006, 589. Fimiani also reports that the study "shows a synergistic effect of terlipressin when added to albumin and diuretics in patients with refractory ascites." *Id.*; *see also id.* at 587 (Abstract) ("In conclusion, our study shows a synergistic effect of terlipressin [versus] treatment with albumin plus diuretics in patients with refractory ascites.").

We observe that the overriding factor in the Federal Circuit's decision was the extremely high degree of failure in the art of treating NSCLC—i.e., a 99.5% failure rate. *OSI Pharms.*, 939 F.3d at 1385. That factor combined with the lack of any evidence in the record that erlotinib *could* treat NSCLC led the Federal Circuit to conclude that an ordinarily skilled artisan would have expected failure rather than success. *Id.* But here, Patent Owner does not point us to any comparable failure rate in the art. The record instead supports Petitioner's contentions about terlipressin's efficacy in treating ascites. For example, Hsu[13] cites to Fimiani's results as "suggest[ing] that the combination of terlipressin and albumin controlled ascites better than the combination of diuretics and albumin." Ex. 1015, 125; *see also* Ex. 1007, 1 (press release describing the FDA's approval of "orphan-drug designation for terlipressin for the treatment of ascites"); Ex. 1020, 1515 (reporting that "treatment with [terlipressin] could beneficially affect water handling and the prognosis" of patients with cirrhosis and ascites without hyponatremia or HRS).

[13] Shao-Jung Hsu and Hui-Chun Huang, *Management of ascites in patients with liver cirrhosis: Recent evidence and controversies*, 76 J. CHINESE MED. ASS'N. 123–130 (2013) ("Hsu," Ex. 1015).

For these reasons, we agree with Petitioner that *OSI Pharmaceuticals* is inapposite to the facts of this case.

3. Additional considerations

We must consider any evidence of objective indicia of non-obviousness before reaching our conclusion on obviousness *vel non*. *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1328 (Fed. Cir. 2016). Patent Owner presents arguments styled as "additional considerations" that purport to support the non-obviousness of the claimed invention. PO Resp. 58–60. First, Patent Owner argues that the claimed invention satisfies a long-felt, but unmet, need. *Id.* at 58–59. Second, Patent Owner argues that Petitioner's own failure to adopt continuous infusion over bolus administration of terlipressin in Petitioner's ongoing clinical trials "further demonstrates that the invention would not have been obvious to [an ordinarily skilled artisan] at the time of the invention." *Id.* at 59–60.

a) Nexus and evidence

At the outset, we give Patent Owner's arguments about long-felt, but unmet, need no weight in our obviousness analysis. "For objective evidence of secondary considerations to be accorded substantial weight, its proponent must establish a nexus between the evidence and the merits of the claimed invention." *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011) (quotation and emphasis omitted). Here, not only does Patent Owner fail to provide any evidence that the claimed invention satisfies a long-felt, but unmet, need, Patent Owner also does not allege (or mention) a "nexus." PO Resp. 58–59. And this is not a case where we apply a presumption of nexus, because Patent Owner has not shown or alleged a specific commercial product that is the invention disclosed and claimed in the '945

patent. *Id.*; *see also WBIP*, 829 F.3d at 1329 (setting forth circumstances in which the presumption of nexus applies). But even if we assume a nexus, Patent Owner does not direct us to any persuasive evidence of a long-felt, but unmet, need. Specifically, Patent Owner makes no specific argument beyond asserting that "Fimiani is the only paper identified that reported the effect of a terlipressin-containing treatment regimen on ascites." PO Resp. 59. Thus, we find no persuasive evidence that the claimed invention fulfills a long-felt need, and no nexus to the claimed invention.

b) Petitioner's CONFIRM trial

Patent Owner's argument that Petitioner's actions support the non-obviousness of the claimed invention is also unpersuasive. Patent Owner points to Petitioner's "CONFIRM" trial, a clinical trial to "Confirm Efficacy and Safety of Terlipressin in Subjects with [HRS] Type 1." PO Resp. 59–60 (citing Ex. 2006, 2; Ex. 2005, 3). Patent Owner argues that, "[i]f Robertson and Angeli 2013 provided motivation to change from bolus infusion to continuous infusion for cost, convenience, safety, and efficacy reasons," then Petitioner "would have adopted continuous infusion over bolus dosing in its ongoing clinical trial." *Id.* at 59. That Petitioner did not adopt continuous infusion, Patent Owner argues, "further demonstrates that the invention would not have been obvious." *Id.* at 60 (citing Ex. 2023 ¶ 143).

We find that Patent Owner's argument lacks sufficient and credible evidence showing that Petitioner's failure to follow the path set out by the references was due to "technical reasons why the combination [of prior art references] would not have been obvious." *In re Nilssen*, 837 F.2d 1098 (Fed. Cir. 1987). The only evidence Patent Owner provides is Dr. Bosch's declaration, which merely states that Petitioner's clinical trial utilized

"repeated bolus dosing instead of continuous infusion." Ex. 2023 ¶ 143. Thus, the record contains no evidence as to whether Petitioner's actions were the result of technical infeasibility, business reasons, or something else. For this reason, Patent Owner's argument is not persuasive as to non-obviousness. *Cf. Orthopedic Equip. Co. v. United States*, 702 F.2d 1005, 1013 (Fed. Cir. 1983) ("[T]he fact that the two disclosed apparatus would not be combined by business[wo]men for economic reasons is not the same as saying that it could not be done because skilled persons in the art felt that there was some technological incompatibility that prevented their combination. Only the latter fact is telling on the issue of nonobviousness.").

4. Conclusion as to obviousness over Fimiani and Robertson or Angeli

In sum, we find that the combination of Fimiani and Robertson or Angeli teaches or suggests each and every element of claims 1–14. We find that an ordinarily skilled artisan would have been motivated to combine Fimiani with Robertson or Angeli, and would have had a reasonable expectation of success in achieving the claimed invention. We also find that Patent Owner has failed to persuasively show secondary considerations of non-obviousness. Thus, after carefully considering the arguments and evidence, we determine that the record as a whole weighs in favor of a conclusion of obviousness, especially given the disclosures of the art of record in this case and strength of the obviousness case based on the first three *Graham* factors.

G. Petitioner's Remaining Grounds of Unpatentability

Our determination that Petitioner has demonstrated, by a preponderance of the evidence, that claims 1–14 would have been obvious over Fimiani and Robertson or Angeli involves all challenged claims of the '945 patent. Thus, we need not address Petitioner's grounds of unpatentability based on obviousness of claims 7, 8, and 10 over Robertson, Pet. 25–28, or obviousness of claims 1, 2, 6, and 12 over Angeli, Pet. 28–35. *See, e.g.*, *Nippon Suisan Kaisha Ltd. v. Pronova Biopharma Norge AS*, PGR2017-00033, Paper 37 at 27 (PTAB Jan. 16, 2019) (citing *SAS Inst. Inc. v. Iancu*, 138 S. Ct. 1348, 1359 (2019) (holding that a petitioner "is entitled to a final written decision addressing all of the claims it has challenged"); *Beloit Corp. v. Valmet Oy*, 742 F.2d 1421, 1423 (Fed. Cir. 1984) (holding that once a dispositive issue is decided, there is no need to decide other potentially dispositive issues)).

IV. PATENT OWNER'S CONTINGENT MOTION TO AMEND

We have concluded that the challenged claims of the '945 patent are unpatentable. Therefore, we address Patent Owner's contingent motion to enter proposed substitute claims 15–28. Mot. Amend 1.

A. Proposed Substitute Claims

Patent Owner proposes to substitute claims 15–28 for claims 1–14, should claims 1–14 be held unpatentable. Mot. Amend 1. Specifically, Patent Owner proposes substitute claim 15 as set forth below, with additions shown in underlining.

> 15. A method for treating <u>ascites in</u> a patient diagnosed with ascites due to liver cirrhosis, the method comprising administering terlipressin or salt thereof as a continuous infusion dose of about 1.0 mg to about 12.0 mg per day to the patient for

about one day to about 12 months.

Id. at 3. Proposed claims 16–20 substitute for claims 2–6, respectively, and depend from proposed substitute claim 15. *Id.* at 4–5. Claim 7 is renumbered as proposed substitute claim 21, and proposed substitute claims 22–25 and 28 (which substitute for claims 8–11 and 14, respectively) depend from claim 21. *Id.* at 5–7. Finally, proposed substitute claims 26 and 27 substitute for claims 12 and 13, respectively. *Id.* at 6–7. Claim 26 depends from proposed substitute claim 15, and claim 27 depends from proposed substitute claim 26. *Id.* Proposed substitute claim 26 (former claim 12) recites "the patient." *Id.*; *see also supra* § III.C.2.

B. Statutory and Regulatory Requirements

In reviewing a motion to amend, we must first consider whether the motion meets the statutory and regulatory requirements set forth in 35 U.S.C. § 316(d) (2012) and 37 C.F.R. § 42.121 (2019). *Lectrosonics, Inc. v. Zaxcom, Inc.*, IPR2018-01129, Paper 15 at 4 (PTAB Feb. 25, 2019) (precedential) ("*Lectrosonics*"). In this regard, the patent owner must demonstrate that the amendment proposes a reasonable number of substitute claims, responds to a ground of unpatentability involved in the trial, does not seek to enlarge the scope of the claims of the patent or introduce new subject matter, and that the proposed claims are supported in the original disclosure of the patent as well as any earlier-filed disclosure for which a priority benefit is sought. *See* 35 U.S.C. § 316(d) (2012); 37 C.F.R. § 42.121 (2019); *see also Lectrosonics*, Paper 15 at 4–8.

1. Reasonable number of substitute claims

The Motion to Amend must propose a reasonable number of substitute claims. 35 U.S.C. § 316(d)(1)(B) (2012). "There is a rebuttable

presumption that a reasonable number of substitute claims per challenged claim is one (1) substitute claim." *Lectrosonics*, Paper 15 at 4 (citing 37 C.F.R. § 42.121(a)(3)). The Petition challenges 14 claims (claims 1–14), and at most, the Motion to Amend proposes 14 claims (substitute claims 15–28). Mot. Amend 1. Thus, we determine that the number of proposed claims is reasonable.

2. Responsiveness to a ground of unpatentability

The proposed substitute claims must respond to a ground of unpatentability involved in this trial. *Lectrosonics*, Paper 15 at 5. To that end, the Motion to Amend proposes that claim 15 recites "treating ascites in a patient diagnosed with ascites due to liver cirrhosis." Mot. Amend. 3 (addition underlined). Patent Owner argues that "substitute claim 15 (and its dependent claims) responds to the Board's preliminary construction of the preamble language of claim 1 to make explicit that the preamble should be construed as treating a patient for ascites due to liver cirrhosis." *Id.* at 7. We agree with Patent Owner that the proposed addition to claim 15 responds to a ground of unpatentability involved this trial. Specifically, "treating ascites in a patient diagnosed with ascites due to liver cirrhosis" makes clear that the purpose of terlipressin administration is to treat ascites itself. *See supra* § III.C.1. Because the parties debate whether Robertson teaches treating ascites itself (versus treating a patient diagnosed with ascites), proposed substitute claim 15 responds to Petitioner's unpatentability ground for anticipation by Robertson.[14]

[14] Moreover, we note that Petitioner's counsel acknowledged during oral hearing that, if the claims are amended to treat ascites, then Robertson

3. Change in scope of the claims; new matter

"A motion to amend may not present substitute claims that enlarge the scope of the claims of the challenged patent or introduce new subject matter." *Lectrosonics*, Paper 15 at 6 (citing 35 U.S.C. § 316(d)(3); 37 C.F.R. § 42.121(a)(2)(ii)).

a) No enlargement

"A substitute claim will meet the requirements of § 42.121(a)(2)(i) and (ii) if it narrows the scope of at least one claim of the patent, for example, the challenged claim it replaces, in a way that is responsive to a ground of unpatentability involved in the trial." *Lectrosonics*, Paper 15 at 6–7. Patent Owner argues that "proposed substitute claim 15 narrows the scope to explicitly require treating a patient *for* ascites due to liver cirrhosis," proposed substitute claim 26 is amended "to improve the clarity of the claim" by adding the definite article "the" before "patient," and the remaining claims "are unchanged relative to their original form except to update the claim number and/or identification of the claim from which they depend." Mot. Amend 1–2. Petitioner does not challenge this aspect of the proposed substitute claims. *See generally* Opp. Mot. Amend. We agree with Patent Owner that the proposed substitute claims do not enlarge the scope of the claims. Only claim 15 contains a substantive amendment, and, as noted above, that amendment narrows the scope of original claim 1 by making clear that the purpose of terlipressin administration is to treat ascites itself.

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no longer anticipates the claims. *See* Tr. 21:5–9 ("We don't allege Robertson anticipation for the substitute claims.").

b) No new matter

"[T]he Board requires that a motion to amend set forth written description support in the originally filed disclosure of the subject patent for each proposed substitute claim, and also set forth support in an earlier filed disclosure for each claim for which benefit of the filing date of the earlier filed disclosure is sought." *Lectrosonics*, Paper 15 at 7 (citing 37 C.F.R. §§ 42.121(b)(1), 42.121(b)(2)). Patent Owner provides a claim chart identifying support for each proposed substitute claim in the disclosure of U.S. Application No. 15/198,050 ("the '050 application," Ex. 2043), which issued as the '945 patent, as well as the provisional applications to which the '050 application claims priority: U.S. Provisional Application Number 62/186,638 (Ex. 2040), U.S. Provisional Application Number 62/267,510 (Ex. 2041), and U.S. Provisional Application Number 62/321,558 (Ex. 2042). Mot. Amend 2–7. We have reviewed Patent Owner's claim chart, and are persuaded that Patent Owner has shown that the proposed substitute claims do not introduce new subject matter.

Petitioner contends that the proposed substitute claims lack adequate written description support. Opp. Mot. Amend 21–24; Sur-reply Mot. Amend 10–11. The test for determining compliance with the written description requirement is whether the disclosure of the application as originally filed reasonably conveys to a person of ordinary skill in the art that the inventor had possession at the time of filing of the claimed subject matter, rather than the presence or absence of literal support in the specification for the claim language. *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc); *Vas-Cath, Inc. v. Mahurkar*,

935 F.2d 1555, 1563 (Fed. Cir. 1991); *In re Kaslow*, 707 F.2d 1366, 1375 (Fed. Cir. 1983).

Petitioner contends that the specification of the '945 patent does not describe "that a dose of terlipressin as low as 'about 1.0mg' for as short as 'one day' can treat ascites or reduce the accumulation of ascitic fluid in the abdomen." Opp. Mot. Amend 21. We disagree. The '050 application, which issued as the '945 patent, expressly states that:

> In each of the aspects of the invention, the condition of the patient may not have progressed to HRS. Also, the terlipressin dose may range from *about 1.0 mg* to about 12.0 mg per day, and the terlipressin dose may be escalated over the course of the therapy. In addition, the terlipressin may be administered for a time period of *about 1 day* to about 12 months. Further, the continuous terlipressin may be administered with an ambulatory infusion pump.

Ex. 2042 ¶ 12 (emphases added); s*ee also* Ex. 1001, 2:14–21. Thus, contrary to Petitioner's contentions otherwise, the '050 application describes a terlipressin dose as low as 1.0 mg and a treatment period as short as 1 day. Moreover, the '050 application states that this dose and treatment period applies "[i]n each of the aspects of the invention." *Id.* These aspects include "reducing the volume of ascitic fluid," Ex. 2042 ¶ 6, and "reducing or resolving ascites," *id.* ¶ 14.

Although acknowledging this description, Petitioner contends that "the bare mention of 'about 1.0 mg' and 'about 1 day' in the summary of the invention section does not disclose this combination of dose and duration could be used to treat ascites." Opp. Mot. Amend 23. Petitioner contends that only Example 2 shows the actual treatment of ascites, but even then at the lowest dose of 2 mg and the shortest duration of 10 days. *Id.* at 22.

Petitioner further contends that the Board "should not consider Example 1 as support since Example 1 is only 'expected' to treat ascites." *Id.*

At bottom, Petitioner's argument appears to be that, to satisfy the written description requirement, Patent Owner must provide examples showing that every amount in its disclosed dosage range (about 1.0 mg to about 12 mg per day), in combination with every time period in its duration range (about 1 day to about 12 months), can treat ascites. Petitioner, however, points us to no legal principle or case law citation standing for such a proposition.

The case law is clear that the written description requirement "does not demand either examples or an actual reduction to practice." *Ariad*, 598 F.3d at 1352. Thus, that the '050 application does not provide an actual example of "a terlipressin dose as low as 1.0 mg and a treatment period as short as 1 day" is not dispositive of the written description inquiry. Instead, the test for written description is whether the disclosure "conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Id.* at 1351. Petitioner points to no credible and persuasive evidence that an ordinarily skilled artisan would not have understood the applicant to have been in possession of the claimed dosage and time period ranges disclosed in the '050 application. *See* Opp. Mot. Amend 21–24.

For these reasons, we agree with Patent Owner that the proposed substitute claims do not introduce new matter and are adequately supported by the original disclosure of the '945 patent (i.e., the '050 application).

4. Claim listing

The Motion to Amend includes a claim listing, as required by 37 C.F.R. § 42.121(b). *Lectrosonics*, Paper 15 at 8; Mot. Amend 28–31 (App'x A).

5. Summary

In view of the above, we determine that Patent Owner's Contingent Motion to Amend meets the statutory and regulatory requirements of 35 U.S.C. § 316(d) and 37 C.F.R. § 42.121 in a manner sufficient such that Petitioner has the burden of persuasion with respect to patentability.

C. Patentability of the Proposed Substitute Claims

Next, we consider patentability. To begin, we note that the patent owner "does not bear the burden of persuasion to demonstrate the patentability of [the proposed] substitute claims." *Lectrosonics*, Paper 15 at 4 (citing *Aqua Prods., Inc. v. Matal*, 872 F.3d 1290 (Fed. Cir. 2017); *Bosch Auto. Serv. Sols. LLC v. Iancu*, 878 F.3d 1027 (Fed. Cir. 2017)). "Rather, as a result of the current state of the law and [U.S. Patent and Trademark Office] rules and guidance, the burden of persuasion will ordinarily lie with the petitioner to show that any proposed substitute claims are unpatentable by a preponderance of the evidence." *Lectrosonics*, Paper 15 at 4.

Petitioner challenges the patentability of proposed substitute claims 15–28 on the following two grounds:

Claims	35 U.S.C. §	Reference(s)
15–28	103	Fimiani and Robertson or Angeli
15–17, 19, 21, 22, 24	103	Robertson

Opp. Mot. Amend 2–21. Specifically, Petitioner contends that the proposed substitute claims would have been obvious over Fimiani and Robertson or

Angeli for essentially the same reasons Petitioner provides in connection with claims 1–14. *See* Opp. Mot. Amend 2 ("[T]he Petition already explained how Fimiani in view of Robertson or Angeli renders obvious 'treating ascites' in addition to the un-amended limitations of the substitute claims."). After considering the entirety of the record before us, we determine that Petitioner shows by a preponderance of the evidence that substitute claims 15–28 are unpatentable as having been obvious over Fimiani and Robertson or Angeli. Because we determine that all proposed substitute claims are unpatentable over Fimiani and Robertson or Angeli, we decline to address Petitioner's ground of unpatentability based on obviousness over Robertson.

1. Limitations of claim 15

We focus our analysis on claim 15—the only proposed substitute claim that contains a substantive difference from its original claim. As explained above, the preamble of proposed substitute claim 15 recites a method for "treating ascites in a patient diagnosed with ascites due to liver cirrhosis." Mot. Amend. 3 (addition underlined). Thus, unlike claim 1 of the '945 patent, discussed *supra* § III.C.1, the preamble of proposed substitute claim 15 is limited to the treatment of ascites itself, in a patient diagnosed with ascites due to liver cirrhosis.

Fimiani, however, teaches the treatment of ascites in a patient diagnosed with ascites due to liver cirrhosis. Specifically, Fimiani discloses the treatment of 26 cirrhotic patients with refractory ascites without HRS. Ex. 1006, 587 (Abstract). Of those patients, 16 had "HCV-related cirrhosis," 2 had "HBV-related" cirrhosis, and 7 had "alcohol cirrhosis." *Id.* at 588. "[A]ll the patients had tense (grade 3) ascites." *Id.* We credit and

rely on Dr. Gow's unrebutted testimony that the ordinarily skilled artisan would have understood that "the refractory ascites of the 'cirrhotic patients' was due to the patients having liver cirrhosis." Ex. 1002 ¶ 146.

Fimiani also teaches treating those patients with a bolus administration of terlipressin of 0.5 mg every 6 hours (i.e., 2 mg/day), with a progressive increase up to 1 mg qid (i.e., 4 mg/day) for three weeks. Ex. 1006, 588; Ex. 1002 ¶¶ 151–152. Thus, Fimiani discloses both the claimed amount of terlipressin (about 1.0 mg to about 12.0 mg per day) and the claimed duration of treatment (about one day to about 12 months). Although Fimiani does not disclose the claimed route of administration, i.e., "continuous infusion," as explained above as to claims 1–14, Robertson teaches continuous terlipressin administration as an alternative to bolus administration "with similar efficacy and often using a lower total dose, representing a potential cost saving." Ex. 1004, 2125. And Angeli teaches "continuous intravenous infusion" of terlipressin, at an initial dose of 2 mg/day to a maximum dose of 12 mg/day, with the length of treatment usually between 10 to 15 days. Ex. 1005, 242.

Patent Owner repeats its argument that Fimiani does not teach or suggest that terlipressin treats ascites or reduces the accumulation of ascitic fluid in the abdominal cavity in an ambulatory ascites patient with terlipressin. *See* Mot. Amend 16–19. Specifically, Patent Owner argues that, because Fimiani did not use necessary controls, Fimiani could only speculate that the combination of terlipressin, diuretics, and albumin "might improve patient outcomes." *Id.* at 16–18. And, Patent Owner argues, given the prior art teaching that albumin treats ascites, an ordinarily skilled artisan

would not have concluded that terlipressin treats ascites based on the data in Fimiani. *Id.* at 17–18.

We disagree. Fimiani reports that terlipressin improved the outcome of refractory ascites in patients without HRS and reduced ascetic fluid in the abdominal cavity. Ex. 1006, 589. Specifically, Fimiani observed improvement in the severity of ascites, a reduction in body weight, increase in urinary sodium excretion, and a reduction of abdominal circumference of at least 10% in 16 of 26 patients administered diuretics, albumin, and terlipressin. *Id.* at 588. And Fimiani expressly states that these observed improvements result from the "synergistic effect *of terlipressin* when added to albumin and diuretics in patients with refractory ascites." *Id.* at 589 (emphasis added); *see also id.* at 587 (Abstract) ("In conclusion, our study shows a synergistic effect of terlipressin [versus] treatment with albumin plus diuretics in patients with refractory ascites.").

Moreover, even if Fimiani did not use appropriate controls, we must consider the reference for all that it teaches. Fimiani clearly teaches "a synergistic effect of terlipressin when added to albumin and diuretics in patients with refractory ascites." Ex. 1006, 589 (Abstract). Fimiani also *expressly encourages* skilled artisans to undertake further "prospective, randomized controlled studies . . . to confirm our preliminary data." *Id.* at 589. As we explained above, this disclosure is a sufficient teaching or suggestion of treating a patient with terlipressin as claimed, which is all the law requires.

2. Motivation to combine

Upon review of the complete record, we reiterate that the record establishes by a preponderance of the evidence that an ordinarily skilled

artisan would have been motivated to combine the teachings of Fimiani and Robertson or Angeli; that is, to substitute the bolus method of terlipressin administration in Fimiani with the continuous infusion method of terlipressin administration of Robertson or Angeli. *See* Opp. Mot. Amend 11–16. Again, Fimiani expressly encourages skilled artisans to undertake further "prospective, randomized controlled studies . . . to confirm [its] preliminary data" that terlipressin, when added to the albumin and diuretics standard therapy in patients with refractory ascites, produces a synergistic effect. Ex. 1006, 589. We agree with Petitioner than an ordinarily skilled artisan undertaking those experiments—and looking to improve administration of terlipressin to ascites patients—would have had a reason to look to Robertson or Angeli. Opp. Mot. Amend 11.

Robertson expressly suggests using continuous terlipressin infusion as a replacement for bolus administration (as Fimiani teaches) to reduce costs. Ex. 1004, 2125. Robertson also expressly suggests administering continuous terlipressin infusion on an outpatient basis (i.e., an ambulatory or non-hospitalized patient), as recited in claim 7. *Id.* Indeed, Robertson explains that "[m]ultiple case reports now exist describing continuous terlipressin infusion as an alternative to intravenous bolus administration, with similar efficacy and often using a lower total dose, representing a potential cost saving." Ex. 1004, 2125. The objective of Robertson's study was to show that, although "[t]erlipressin is traditionally given using a bolus regimen in a hospital setting," the administration of continuous terlipressin in an outpatient setting is not only "feasible," but also "efficacious[] and well tolerated." *Id.* at 2125–26. Thus, Robertson "present[s] the first reported case of an outpatient continuous terlipressin infusion for treatment

of recurrent HRS as a bridge to successful liver transplantation." *Id.* at 2125.

Given Robertson's successful results, we agree with Petitioner that an ordinarily skilled artisan would have been motivated to treat the patient population studied in the clinical trial of Fimiani with continuous terlipressin infusion, as recited in proposed substitute claim 15. We also note that Robertson's terlipressin administration (i.e., 3 mg/day for 22 days as an outpatient) overlaps with the dosage ranges and durations Fimiani teaches (i.e., 2 to 4 mg/day for three weeks). These factors together persuade us that an ordinarily skilled artisan would have been motivated to substitute the bolus method of terlipressin administration in Fimiani with the continuous infusion method of terlipressin administration in Robertson. The combination of references provides cost savings in the amount of terlipressin needed. Ex. 1004, 2125–26; Ex. 1002 ¶ 159.

For the same reasons, we also agree with Petitioner that an ordinarily skilled artisan would have had a reason to substitute Fimiani's bolus administration with Angeli's continuous infusion. Opp. Mot. Amend 11. Angeli states that "terlipressin given by continuous intravenous infusion is more effective and better tolerated than when it is given by intravenous boluses," Ex. 1005, 241, that "the use of terlipressin by continuous intravenous infusion may turn out to be safer and cheaper than that by continuous intravenous boluses," and that terlipressin may be used in "lower dose[s]" when administered "by continuous intravenous infusion rather tha[n] when it is given by intravenous boluses," *id.* at 245. Thus, we find that Angeli provides express motivation to substitute Fimiani's bolus administration with continuous terlipressin infusion—i.e., because

continuous infusion is more effective, better tolerated, safer, and cheaper. *See* Ex. 1002 ¶ 216. We also note that Angeli, like Robertson, teaches terlipressin administration of 2 mg/day to 12 mg/day for 10–15 days, which overlaps with the dosage ranges and durations Fimiani teaches, further supporting Petitioner's reason to combine.

Moreover, we find credible, and supported with record evidence, Dr. Gow's unrebutted testimony that it was well known in the art that ascites develops when there is severe portal hypertension. Ex. 2002 ¶ 217; *see also* Ex. 1006, 587 (stating that ascites "develops late during the course of [liver cirrhosis], when there are severe portal hypertension and hepatic insufficiency"). Angeli teaches that the use of intravenous boluses to administer terlipressin (which typically occurred every 4 to 6 hours) "does not appear to be the best way of maximizing the effect of terlipressin" because "the effect of terlipressin on portal pressure has been shown to last less than 4 h[ours]." Ex. 1005, 245. Given the relationship between ascites and portal hypertension, Angeli's teachings would have provided the ordinarily skilled artisan with an additional reason to substitute Fimiani's bolus administration with continuous infusion of terlipressin—i.e., to maximize the effectiveness of terlipressin on portal pressure. Ex. 1006, 587; Ex. 1002 ¶ 217.

Patent Owner argues that an ordinarily skilled artisan would not have been motivated to combine Fimiani with Robertson or Angeli for the same reasons discussed above in connection with claims 1–14. Again, these arguments are not persuasive, as we explain above. *Supra* § III.F.2.a.

3. Reasonable expectation of success

We also find that ordinarily skilled artisan would have had a reasonable expectation that using Robertson's or Angeli's continuous infusion administration would have been successful in treating ascites in a patient diagnosed with ascites due to liver cirrhosis, as recited in proposed substitute claim 15. Again, we find that an ordinarily skilled artisan would have reasonably expected continuous infusion of terlipressin to be successful, because both Fimiani and each of Robertson and Angeli use overlapping doses of terlipressin and both report improved renal function in their respective patient populations. Ex. 1002 ¶¶ 158, 224.

Patent Owner's arguments in opposition are the same as discussed above, and are not persuasive for the reasons explained. *Supra* § III.F.2.b. In addition, Patent Owner, relying on Dr. Bosch's declaration, argues that an ordinarily skilled artisan would not have had a reasonable expectation of success given "differences in the pharmacokinetic (PK) profile of the plasma concentrations associated with bolus and continuous infusion terlipressin dosing." Reply Mot. Amend (citing Ex. 2044 ¶ 6). Dr. Bosch testifies that "the PK profiles for bolus and continuous terlipressin dosing are very different since the bolus dosing results in repeated spikes and troughs of plasma concentration of terlipressin whereas continuous infusion dosing provides steady state plasma concentrations at much lower levels than the repeated spikes." Ex. 2044 ¶ 6.

We view this testimony, however, as supporting Petitioner's argument that an ordinarily skilled artisan would have had a reason to substitute Fimiani's bolus administration with Robertson's or Angeli's continuous infusion administration. Specifically, the steady dosage achievable with

continuous infusion improves safety and reduces the costs of administering terlipressin. *See, e.g.*, Ex. 1002 ¶¶ 149–150, 158, 177, 216, 247. Indeed, Robertson explains that "[m]ultiple case reports now exist describing continuous terlipressin infusion as an alternative to intravenous bolus administration, with similar efficacy and often using a lower total dose, representing a potential cost saving." Ex. 1004, 2125. Angeli also states that "the use of terlipressin by continuous intravenous infusion may turn out to be safer and cheaper than that by continuous intravenous boluses," because terlipressin may be used in "lower dose[s]" when administered "by continuous intravenous infusion rather tha[n] when it is given by intravenous boluses." Ex. 1005, 241, 245.

4. Additional considerations

Patent Owner repeats its arguments styled as "additional considerations" that purport to support the non-obviousness of the claimed invention. Again, these arguments are not persuasive for the reasons explained above. *Supra* § III.F.3.

D. Conclusion on Motion to Amend

Based on the evidence in the entire trial record, we determine that Petitioner has shown by a preponderance of the evidence that the proposed substitute claims would have been obvious over Fimiani and Robertson or Angeli. Accordingly, Patent Owner's Motion to Amend is denied.

V. CONCLUSION[15]

Petitioner establishes by a preponderance of the evidence that claims 1–14 of the '945 patent are unpatentable as follows.

Claims	35 U.S.C. §	Reference(s)	Claims Shown Unpatentable	Claims Not Shown Unpatentable
1–3, 5	102	Robertson	1–3, 5	
1–14	103	Fimiani, Robertson	1–14	
1–14	103	Fimiani, Angeli	1–14	
Overall Outcome			1–14	

Further, based on the entirety of the record, we determine that proposed substitute claims 15–28 are unpatentable by a preponderance of the evidence based on 35 U.S.C. § 103 over Fimiani and Robertson or Angeli.

Motion to Amend Outcome	Claims
Original Claims Cancelled by Amendment	1–14
Substitute Claims Proposed in the Amendment	15–28
Substitute Claims: Motion to Amend Granted	
Substitute Claims: Motion to Amend Denied	15–28
Substitute Claims: Not Reached	

[15] Should Patent Owner wish to pursue amendment of the challenged claims in a reissue or reexamination proceeding subsequent to the issuance of this decision, we draw Patent Owner's attention to the *Notice Regarding Options for Amendments by Patent Owner Through Reissue or Reexamination During a Pending AIA Trial Proceeding*, 84 Fed. Reg. 16,654 (Apr. 22, 2019). If Patent Owner chooses to file a reissue application or a request for reexamination of the challenged patent, we remind Patent Owner of its continuing obligation to notify the Board of any such related matters in updated mandatory notices. *See* 37 C.F.R. § 42.8(a)(3), (b)(2) (2017).

VI. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1–14 of the ’945 Patent have been proven to be unpatentable;

FURTHER ORDERED that Patent Owner’s Motion to Amend is denied;

FURTHER ORDERED that Petitioner’s Motion to Strike is granted-in-part; and

FURTHER ORDERED that because this is a Final Written Decision, parties to the proceeding seeking judicial review of the Decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

FOR PETITIONER:

James Murphy
Johnathan Kirley
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