

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

UNITED THERAPEUTICS CORPORATION,
Petitioner,

v.

ACTELION PHARMACEUTICALS, LTD.,
Patent Owner.

Case IPR2025-01139
U.S. Patent No. 8,268,847

PETITION FOR INTER PARTES REVIEW
U.S. PATENT NO. 8,268,847

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Patent Trial and Appeal Board
U.S. Patent and Trademark Office
PO Box 1450
Alexandria, VA 22313-1450

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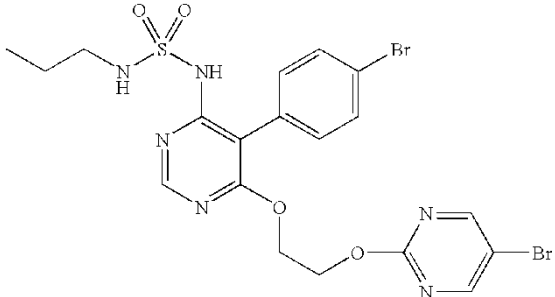
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EX1001	U.S. Patent No. 8,268,847 to Clozel (“’847 patent”)
EX1002	Prosecution History of the ’847 patent
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EX1022	Gregory D. Lewis et al., <i>Sildenafil Improves Exercise Hemodynamics and Oxygen Uptake in Patients with Systolic Heart Failure</i> , 115 CIRCULATION 59 (2007)
EX1023	Alison Keith, <i>The Economics of Viagra®</i> , 19 HEALTH AFF. 147 (2000)
EX1024	Martin H. Bolli et al., <i>The Discovery of N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-propylsulfamide (Macitentan), an Orally Active, Potent Dual Endothelin Receptor Antagonist</i> , 55 J. MED. CHEMISTRY 7849 (2012) (“Bolli 2012”)
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LISTING OF CHALLENGED CLAIMS

Claim 1	
[1.Preamble]	1. A product containing
[1.1]	the compound of formula (I) below (I)  in free or pharmaceutically acceptable salt form,
[1.2]	in combination with at least one compound having PDE5-inhibitory properties, in free or a pharmaceutically acceptable salt form,
[1.3]	for therapeutic use, simultaneously, separately or over a period of time, in the treatment of a disease wherein vasoconstriction is involved.
Claim 2	
[2]	2. The product according to claim 1, wherein the compound having PDE5-inhibitory properties is selected from sildenafil, vardenafil, tadalafil and udenafil.
Claim 3	
[3]	3. The product according to claim 2, wherein the compound having PDE5-inhibitory properties is tadalafil.
Claim 4	
[4]	4. The product according to claim 2, wherein the compound having PDE5-inhibitory properties is sildenafil.
Claim 5	
[5]	5. The product according to claim 1, wherein the disease wherein vasoconstriction is involved is selected from hypertension, pulmonary hypertension, diabetic arteriopathy, heart failure, erectile dysfunction and angina pectoris.
Claim 6	
[6.Preamble]	6. A pharmaceutical composition containing
[6.1]	as active principles, the compound of formula (I) as described in claim 1, in free or pharmaceutically acceptable salt form,

[6.2]	in combination with at least one compound having PDE5-inhibitory properties, in free or pharmaceutically acceptable salt form,
[6.3]	as well as at least one excipient.
Claim 7	
[7]	7. The pharmaceutical composition according to claim 6, wherein the compound having PDE5-inhibitory properties is selected from sildenafil, vardenafil, tadalafil and udenafil.
Claim 8	
[8]	8. The pharmaceutical composition according to claim 7, wherein the compound having PDE5-inhibitory properties is tadalafil.
Claim 9	
[9]	9. The pharmaceutical composition according to claim 7, wherein the compound having PDE5-inhibitory properties is sildenafil.
Claim 10	
[10.Preamble]	10. A method for the treatment of hypertension or pulmonary hypertension comprising
[10.1]	administering to a patient in need thereof an effective amount of a compound of formula (I) as described in claim 1, in free or pharmaceutically acceptable salt form,
[10.2]	in combination with at least one compound having PDE5-inhibitory properties, in free or pharmaceutically acceptable salt form.
Claim 11	
[11]	11. The method according to claim 10, wherein the compound having PDE5-inhibitory properties is selected from sildenafil, vardenafil, tadalafil and udenafil.
Claim 12	
[12]	12. The method of claim 11, wherein the compound having PDE5-inhibitory properties is tadalafil.
Claim 13	
[13]	13. The method of claim 11, wherein the compound having PDE5 inhibitory properties is sildenafil.
Claim 14	
[14]	14. The method of claim 12, wherein the method is for the treatment of pulmonary hypertension.

Claim 15	
[15]	15. The method of claim 14, wherein the pulmonary hypertension is pulmonary arterial hypertension.
Claim 16	
[16]	16. The method of claim 13, wherein the method is for the treatment of pulmonary hypertension.
Claim 17	
[17]	17. The method of claim 16, wherein the pulmonary hypertension is pulmonary arterial hypertension.
Claim 18	
[18]	18. The method of claim 15, wherein the compound of formula (I) and tadalafil are administered simultaneously.
Claim 19	
[19]	19. The method of claim 15, wherein the compound of formula (I) and tadalafil are administered separately.
Claim 20	
[20]	20. The method of claim 15, wherein the compound of formula (I) and tadalafil are administered over a period of time.
Claim 21	
[21]	21. The method of claim 20, wherein the interval between the administration of the compound of formula (I) and the administration of tadalafil does not exceed two days.
Claim 22	
[22]	22. The method of claim 21, wherein the interval does not exceed one day.
Claim 23	
[23]	23. The method of claim 15, where in the compound of formula (I) is administered in a dose of 0.05 mg to 2 mg per kilogram of patient body weight.
Claim 24	
[24]	24. The method of claim 23, wherein tadalafil is administered in a dose of 0.01 mg to 1 mg per kilogram of patient body weight.
Claim 25	
[25]	25. The method of claim 15, wherein the compound of formula (I) is administered in a dose of 0.1 mg to 1 mg per kilogram of patient body weight.

Claim 26	
[26]	26. The method of claim 18, wherein the compound of formula (I) is administered in a dose of 0.05 mg to 2 mg per kilogram of patient body weight.
Claim 27	
[27]	27. The method of claim 26, wherein tadalafil is administered in a dose of 0.01 mg to 1 mg per kilogram of patient body weight.
Claim 28	
[28]	28. The method of claim 18, wherein the compound of formula (I) is administered in a dose of 0.1 mg to 1 mg per kilogram of patient body weight.
Claim 29	
[29]	29. The method of claim 20, wherein the compound of formula (I) is administered in a dose of 0.05 mg to 2 mg per kilogram of patient body weight.
Claim 30	
[30]	30. The method of claim 29, wherein tadalafil is administered in a dose of 0.01 mg to 1 mg per kilogram of patient body weight.
Claim 31	
[31]	31. The method of claim 20, wherein the compound of formula (I) is administered in a dose of 0.1 mg to 1 mg per kilogram of patient body weight.
Claim 32	
[32]	32. The method of claim 21, wherein the compound of formula (I) is administered in a dose of 0.05 mg to 2 mg per kilogram of patient body weight.
Claim 33	
[33]	33. The method of claim 32, wherein tadalafil is administered in a dose of 0.01 mg to 1 mg per kilogram of patient body weight.
Claim 34	
[34]	34. The method of claim 21, wherein the compound of formula (I) is administered in a dose of 0.1 mg to 1 mg per kilogram of patient body weight.
Claim 35	
[35]	35. The method of claim 22, wherein the compound of formula (I) is administered in a dose of 0.05 mg to 2 mg per kilogram of patient body weight.

Claim 36	
[36]	36. The method of claim 35, wherein tadalafil is administered in a dose of 0.01 mg to 1 mg per kilogram of patient body weight.
Claim 37	
[37]	37. The method of claim 22, wherein the compound of formula (I) is administered in a dose of 0.1 mg to 1 mg per kilogram of patient body weight.
Claim 38	
[38]	38. The method of claim 17, wherein the compound of formula (I) and sildenafil are administered simultaneously.
Claim 39	
[39]	39. The method of claim 17, wherein the compound of formula (I) and sildenafil are administered separately.
Claim 40	
[40]	40. The method of claim 17, wherein the compound of formula (I) and sildenafil are administered over a period of time.
Claim 41	
[41]	41. The method of claim 40, wherein the interval between the administration of the compound of formula (I) and the administration of sildenafil does not exceed two days.
Claim 42	
[42]	42. The method of claim 41, wherein the interval does not exceed one day.
Claim 43	
[43]	43. The method of claim 17, wherein the compound of formula (I) is administered in a dose of 0.05 mg to 2 mg per kilogram of patient body weight.
Claim 44	
[44]	44. The method of claim 43, wherein sildenafil is administered in a dose of 0.1 mg to 2 mg per kilogram of patient body weight.
Claim 45	
[45]	45. The method of claim 17, wherein the compound of formula (I) is administered in a dose of 0.1 mg to 1 mg per kilogram of patient body weight.
Claim 46	
[46]	46. The method of claim 38, wherein the compound of formula (I) is administered in a dose of 0.05 mg to 2 mg per kilogram of patient body weight.

Claim 47	
[47]	47. The method of claim 46, wherein sildenafil is administered in a dose of 0.1 mg to 2 mg per kilogram of patient body weight.
Claim 48	
[48]	48. The method of claim 38, wherein the compound of formula (I) is administered in a dose of 0.1 mg to 1 mg per kilogram of patient body weight.
Claim 49	
[49]	49. The method of claim 40, wherein the compound of formula (I) is administered in a dose of 0.05 mg to 2 mg per kilogram of patient body weight.
Claim 50	
[50]	50. The method of claim 49, wherein sildenafil is administered in a dose of 0.1 mg to 2 mg per kilogram of patient body weight.
Claim 51	
[51]	51. The method of claim 40, wherein the compound of formula (I) is administered in a dose of 0.1 mg to 1 mg per kilogram of patient body weight.
Claim 52	
[52]	52. The method of claim 41, wherein the compound of formula (I) is administered in a dose of 0.05 mg to 2 mg per kilogram of patient body weight.
Claim 53	
[53]	53. The method of claim 52 wherein sildenafil is administered in a dose of 0.1 mg to 2 mg per kilogram of patient body weight.
Claim 54	
[54]	54. The method of claim 41, wherein the compound of formula (I) is administered in a dose of 0.1 mg to 1 mg per kilogram of patient body weight.
Claim 55	
[55]	55. The method of claim 42, wherein the compound of formula (I) is administered in a dose of 0.05 mg to 2 mg per kilogram of patient body weight.
Claim 56	
[56]	56. The method of claim 55, wherein sildenafil is administered in a dose 0.1 mg to 2 mg per kilogram of patient body weight.

Claim 57	
[57]	57. The method of claim 42, wherein the compound of formula (I) is administered in a dose of 0.1 mg to 1 mg per kilogram of patient body weight.

I. INTRODUCTION

The '847 patent is directed to the combination of two prior art compounds: an endothelin receptor type A (ET_A) antagonist known as macitentan¹ and a phosphodiesterase 5 (PDE5) inhibitor. *See* EX1001 (U.S. Patent No. 8,268,847), 1:39-59 (identifying examples of ET_A antagonists and PDE5 inhibitors). The prior art also explicitly teaches combining ET_A antagonists with PDE5 inhibitors—including both generally combining those compounds and combining specific ET_A antagonists with PDE5 inhibitors—for the treatment of vasoconstrictive diseases, such as erectile dysfunction (ED) and hypertension.

There is no novel compound in the claims, no novel dosing, no novel combination, and no novel use. The claims are directed to nothing more than a combination of two known drugs, used for their known therapeutic purposes. EX1001, 1:16-38, claims 1-57. This Petition raises three grounds of unpatentability, including anticipation and obviousness grounds not previously considered by the Patent Office.

Bolli (EX1004) discloses all elements of the claimed combination and therefore anticipates the claims (Ground 1). Secondary considerations are irrelevant

¹ This Petition uses the terms “compound of Formula (I)” and “macitentan” interchangeably because they are the same thing. EX1013, ¶93.

to anticipation and cannot support patentability.

The claims are also obvious over the teachings of Bolli and Keyser (EX1005) (Ground 2) and independently obvious over the teachings of Hoeper (EX1009) along with its corresponding letter to the editor, Morice (EX1010), and Bolli (Ground 3). Patent Owner (“PO”) previously argued in prosecution of the ’847 patent and a related application that Keyser “teaches away” from using macitentan in a combination and that surprising results rescue the claims. Neither argument has merit. The alleged teaching away is at most a mild preference over one particular endothelin receptor (“ET”) antagonist, bosentan, and would not have discouraged the person of ordinary skill in the art (POSA) from using macitentan in the claimed combination. The alleged surprising results similarly fail to salvage the claims for several reasons, including errors of fact and law. For example, the alleged results are not commensurate with the claims, are not actually surprising, and are not properly supported because they rely on post-priority references that cannot change the POSA’s expectations.

United Therapeutics Corporation (“Petitioner”) therefore requests *inter partes* review (IPR) and cancellation of claims 1-57 of the ’847 patent.

II. REASONS TO INSTITUTE

Inter partes review should be instituted because the claims are both anticipated and obvious. Each time patentability of the ’847 patent was examined,

the claims were determined to be *prima facie* obvious over Bolli in view of Keyser. Yet the '847 patent issued because anticipation was not considered. Moreover, PO presented incomplete and meritless teaching away and unexpected results arguments that relied on characterizations about macitentan's properties unavailable as of the priority date, misinterpretation of the prior art, and misapplication of the law.

A. Background

During prosecution, the examiner rejected the claims as obvious over Bolli in view of Keyser, citing Bolli's teaching of macitentan as an ET antagonist and Keyser's teaching of ET antagonist and PDE5 inhibitor combinations. EX1002, 140-41. The examiner erroneously disqualified Bolli as prior art under 35 U.S.C. §103(c)² and—despite the opportunity to correct that error—PO twice wrongfully asserted Bolli did not qualify as prior art. *Id.*, 207, 239. The examiner allowed the claims predicated upon that legal error. *Id.*, 303.

Two weeks before the '847 patent issued, PO filed a continuation with several nearly identical claims.³ EX1006, 1-9. All claims were rejected on several grounds, including obviousness over Bolli and Keyser. *Id.*, 103-21. PO appealed to the PTAB

² It is undisputed that the examiner erroneously considered Bolli to be prior art only under 35 U.S.C. §102(e), when it is, in fact, §102(b) art. *Id.*, 303.

³ U.S. Application No. 13/604,148 ("148 Application").

and argued surprising results.⁴ *Id.*, 378-88. PO asserted Keyser “teaches away from using a compound having non-selective ET activity” (*id.*, 384), relying on a post-priority article. That post-priority article—authored by Actelion employees and disclosing Actelion-sponsored research (“Iglarz”) (EX1011)—purportedly disclosed that macitentan did not meet Keyser’s “requirement” of “selective” ET_A antagonists. EX1006, 385-86 (citing EX1011, 6). The PTAB agreed the claims were *prima facie* obvious, but ultimately reversed the obviousness rejection premised upon the alleged surprising results, based upon Iglarz. EX1006, 458-65. Iglarz, however, does not demonstrate that the POSA knew the information in Iglarz regarding macitentan’s selectivity before the priority date. *Id.* PO also made extensive “lead compound” arguments, which the PTAB correctly noted were “inapposite to this case because the compound of formula (I) is not novel.” *Id.*, 462 n.9.

Five years after the ’847 patent issued—and only after obtaining a favorable decision on appeal in the ’148 Application—PO requested reexamination of claims 1-11 to incorporate the Board’s Decision in the ’148 Application and revisit its previous representations regarding §103(c). EX1003, 1-11, 289. The reexamination specialist found the claims patentable, adopting the PTAB’s reasoning in the ’148

⁴ Despite its successful appeal, Patent Owner abandoned the ’148 Application. EX1006, 528-29.

Application appeal without any independent analysis. *Id.*, 375-77.

B. Prosecution Flaws Justifying Institution of *Inter Partes* Review

The PTAB (and by extension, the reexamination specialist) erred in their unexpected results analysis for several reasons.

First, neither the PTAB nor the examiner considered anticipation, to which unexpected results are irrelevant.

Second, the Office legally erred because the purported surprising results are not commensurate with the breadth of *any* of the challenged claims. The '847 patent discloses only limited data from testing in rats at certain doses, but the claims cover all doses for both drugs in the combination, in any species, and do not claim the alleged surprising results. Data from rats with induced hypertension at limited, specific doses—especially with an undisclosed (and likely small) sample size—does not establish surprising results in all species at all doses for all vasoconstrictive diseases.

Third, the Office legally erred by basing its assessment of how the POSA would have understood the prior art as of the priority date on two post-priority publications—Iglarz and Bolli 2012 (EX1024)—that are indisputably *not* prior art. Unexpected results must be evaluated against the POSA's knowledge and expectations *as of the priority date*, but Iglarz and Bolli 2012 were respectively published in 2008 and 2012, *years* after the earliest purported priority date in 2006.

See Forest Labs v. Sigmapharm Labs, LLC, 918 F.3d 928, 937 (Fed. Cir. 2019) (“While have permitted evidence from after the patent is granted to be considered in assessing whether there are unexpected results, ... the results must be ‘unexpected by one of ordinary skill in the art *at the time of [the] application*[.]’”) (emphasis added) (citations omitted). Moreover, neither Iglarz nor Bolli 2012 describe unexpected results or teach away because these references only confirm that macitentan’s selectivity ratio exceeds the alleged “requirement” in Keyser and are thus irrelevant to secondary considerations. EX1013 ¶368. Iglarz actually confirms the *in vitro* selectivity data the POSA would understand from Bolli.

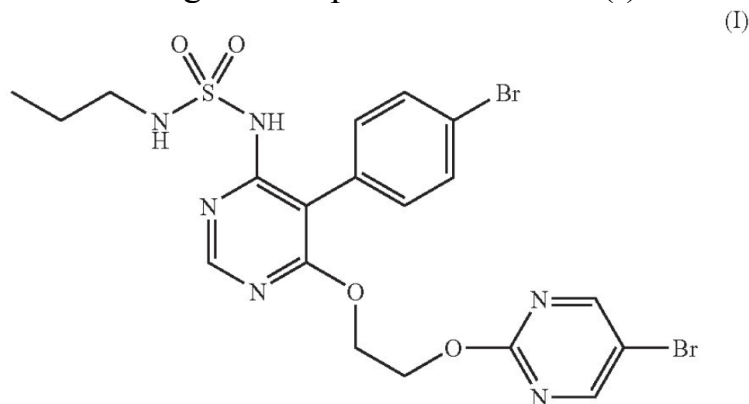
Fourth, the Office erred by relying on PO’s mischaracterization of Keyser. Keyser encouraged the use of compounds more selective than bosentan, but it did not define any “requirements” or “explicit[ly] teach[] away” from macitentan. *Compare* EX1005, [068] *with* EX1002, 205-206. Rather, the POSA would have understood that macitentan was selective for ET_A, and—as the Examiner determined—the POSA would have combined macitentan with a PDE5 inhibitor with a reasonable expectation of successfully treating diseases involving vasoconstriction. *Infra* §V.B.8; *In re Geisler*, 116 F.3d 1465, 1471 (Fed. Cir. 1997) (holding that a preference “falls far short” of teaching away).

III. THE '847 PATENT

A. Summary

The '847 patent describes a combination of a known ET_A antagonist and one or more known PDE5 inhibitors. Claim 1 is representative:

1. A product containing the compound of formula (I) below



in free or pharmaceutically acceptable salt form, in combination with at least one compound having PDE5-inhibitory properties, in free or a pharmaceutically acceptable salt form, for therapeutic use, simultaneously, separately or over a period of time, in the treatment of a disease wherein vasoconstriction is involved.

EX1001, claim 1. The compound of formula (I) is macitentan. EX1013, ¶43. The '847 patent further claims pharmaceutical compositions of formula (I) and a PDE5 inhibitor (EX1001, claims 6-9), and methods of treating hypertension and pulmonary hypertension (*id.*, claims 10-57).

B. Level of Ordinary Skill in the Art

For purposes of this Petition, the POSA would have a Ph.D. in pharmacology or a closely related field, with five years of experience in drug development for cardiovascular and/or pulmonary conditions, experience assessing potential

combination drug products for said conditions, and knowledge of commercially available active ingredients. EX1013, ¶¶21-23. Cardiovascular and/or pulmonary conditions include, *e.g.*, hypertension, pulmonary hypertension (PH), pulmonary arterial hypertension (PAH), diabetic arteriopathy, heart failure, ED, and/or angina pectoris. The POSA would have access to and rely on others in related fields as needed, including, for example, toxicologists, synthetic and medicinal chemists, and clinicians/physicians.

C. Priority Date

Petitioner takes no position on the proper priority date for each claim but conservatively uses August 29, 2006, the earliest filing date to which the '847 patent claims priority, as the priority date. Petitioner therefore assesses the prior art under pre-AIA 35 U.S.C. §102.

D. Claim Construction

Petitioner interprets the '847 patent claims according to the *Phillips* claim construction standard. 37 C.F.R. §42.100(b); *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005). Consistent with that standard, Petitioner interprets the claims and their constituent terms according to their plain and ordinary meaning to the POSA, and adopts and applies the explicit definitions provided in the specification of the '847 patent, including for “simultaneously,” “separately” or “separate,” “over a period of time,” “disease where vasoconstriction is involved,” “compound having

PDE5-inhibitory properties.” EX1001, 2:14-43.

The patent defines simultaneous administration as “by the same route and at the same time.” *Id.*, 2:14-19.

The patent defines separate administration as by different routes of administration at “approximately the same time.” *Id.*, 2:20-24.

The patent defines “over a period of time” as “administration of two or more ingredients at different times,” including administration of a first active ingredient “for several months before administering the other active ingredient or ingredients” such that “no simultaneous administration occurs.” *Id.*, 2:25-35.

The patent defines “disease where vasoconstriction is involved” as “hypertension, pulmonary hypertension (including pulmonary arterial hypertension), diabetic arteriopathy, heart failure, erectile dysfunction or angina pectoris.” *Id.*, 2:36-39.

The patent defines “compound having PDE5-inhibitory properties” as “a compound that ... has an IC₅₀ equal or lower than 1 μM.” *Id.*, 2:40-43.

Beyond the patent’s definitions, Petitioner does not believe, at this time, that any terms require construction to resolve the issues presented herein. EX1013, ¶¶19-20. Petitioner reserves the right to address any claim construction dispute raised during these proceedings.

IV. SCOPE AND CONTENT OF THE PRIOR ART

A. Technical Background

Numerous diseases involve vasoconstriction (narrowed blood vessels), including hypertension, PH, diabetic arteriopathy, heart failure, ED, and angina pectoris. EX1001, 1:42-44; EX1013, ¶¶66-68. Several biological mechanisms are involved in regulating vasoconstriction (and vasodilation), including the endothelin and nitric oxide (NO) pathways. EX1013, ¶¶27-29.

Endothelin is a naturally occurring peptide that is a potent vasoconstrictor. *Id.*, ¶¶26-34. Endothelin comes in different forms (*e.g.*, ET-1, ET-2, or ET-3) that may bind to two receptor subtypes, ET_A and ET_B, with differential affinities. *Id.* These receptors have opposing functions: ET_A receptors primarily mediate vasoconstriction, while ET_B receptors are involved in vasodilation through NO- and prostacyclin-mediated pathways. *Id.*, ¶¶30-31; EX1004, 2. ET antagonists block ET-1 from binding to the receptor to “block the physiological effects of endothelin and are useful in treating patients with endothelin-related disorders.” EX1005, [018]; EX1013, ¶¶26-34. Macitentan is an ET antagonist. EX1013, ¶¶55, 93. By occupying ET_A receptors and blocking endothelin, ET antagonists allow vasodilation and, given the increased ET-1 levels in several vasoconstrictive diseases, ET antagonists have been studied as therapeutic agents. *Id.*, ¶¶26-34.

The NO pathway involves activation of guanyl cyclase by NO to increase

cyclic guanosine monophosphate (cGMP), leading to vasodilation. EX1013, ¶31. The enzyme PDE5 breaks down cGMP. EX1005, [068]; EX1013, ¶35. Inhibiting PDE5 prevents breakdown of cGMP, allowing cGMP to promote vasodilation. Thus, PDE5 inhibitors are vasodilators known to treat conditions involving vasoconstriction. Common PDE5 inhibitors as of the priority date include sildenafil (Viagra®) and tadalafil (Cialis®). EX1013, ¶¶35-36; EX1007; EX1008.

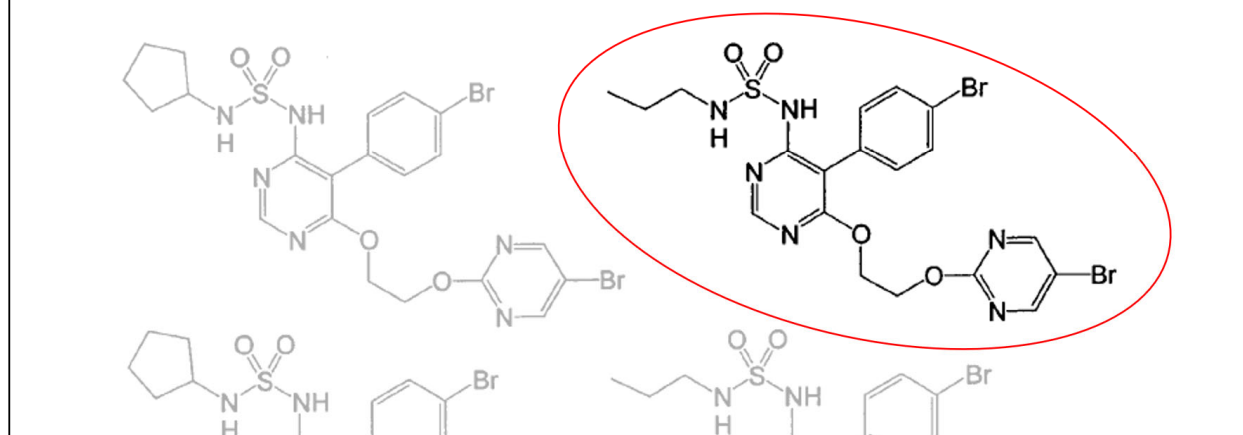
B. Prior Art

1. Bolli (EX1004)

Bolli—published on July 11, 2002—is prior art under 35 U.S.C. §§102(a), (b), and (e). EX1004, [43]. Bolli describes macitentan as a preferred compound for use as an ET antagonist. EX1004, 25, 29.

Bolli describes “novel pyrimidine-sulfamides of general formula I” that can be used in pharmaceutical compositions, and “especially their use as endothelin receptor antagonists.” EX1004, 2. Within general formula I, Bolli teaches an “especially preferred group of compounds” further defined by “formula V,” (*id.*, 22), which includes macitentan:

28



Id., 29 (annotation added).

Bolli also provides IC₅₀ data⁵ evaluating potency and efficacy of various compounds of Formulae I and V. *Id.*, 3-4; *id.*, 1-11, Table 1; EX1013, ¶44. Example 104 is the compound most similar to macitentan—nearly identical—and Table 1 shows it is highly selective for ET_A, with an IC₅₀ of only 0.88, compared to 601 for ET_B. EX1004, 7; EX1013, ¶44. Bolli therefore teaches macitentan is both highly selective and potent. EX1013, ¶44.

Bolli also teaches combining drugs such as macitentan with vasodilators to treat diseases involving vasoconstriction. EX1004, 18.

⁵ IC₅₀ is the abbreviation for “half maximal inhibitory concentration,” which can be used to evaluate potency and selectivity. EX1013, ¶¶39-42. It indicates how much drug is needed to inhibit a biological process by half.

2. Keyser (EX1005)

Keyser—published on March 9, 2006—is prior art under pre-AIA 35 U.S.C. §§102(a) and (e). *Id.*, [43].

Keyser teaches “combination therapies comprising an endothelin A receptor (ET_A) antagonist and a [PDE5] inhibitor ... for the treatment and/or prevention of cardiac disorders such as [PAH].” *Id.*, [002]. Keyser discloses that, while PDE5 inhibitors such as sildenafil are effective for treating PAH, they have several adverse effects and require high doses when administered alone as monotherapies. *Id.*, [009]. To solve this problem, Keyser teaches combining a PDE5 inhibitor with an ET_A antagonist to “act in a complementary fashion ... to provide superior efficacy and/or dosage regimes and/or reduction in side effects.” *Id.*, [067]. Keyser includes data from a pharmacokinetic study showing that the combination of sitaxsentan (an ET_A antagonist) with sildenafil (a PDE5 inhibitor) was well-tolerated. *Id.*, Example 1.

3. Viagra® (EX1007), Revatio® (EX1025), and Cialis® (EX1008)

Food and Drug Administration (FDA) approved sildenafil to treat ED in 1998 (Viagra®) (EX1007, 19) and PAH on June 3, 2005 (Revatio®) (EX1025, 1, 13). FDA approved tadalafil to treat ED in 2003 (Cialis®) (EX1008, 26). The Viagra®, Revatio®, and Cialis® labels were published at approvals and are therefore prior art under pre-AIA 35 U.S.C. §§102(a) and (b). Tadalafil was also studied and used to treat PH. EX1010, 1; EX1019, 6. Sildenafil and tadalafil are PDE5 inhibitors.

EX1007, 1; EX1008, 2.

Sildenafil was patented (U.S. Patent No. 5,250,534) in 1993 (EX1043), and three U.S. pharmacologists who studied its mechanism of action won the 1998 Nobel Prize in Physiology or Medicine “for their discovery that the unstable gas, nitric oxide (NO), is an essential regulator of vasodilation,” (EX1012). Indeed, sildenafil was known to have “vasodilatory properties” that could have an effect on patients with “underlying cardiovascular disease.” EX1007, 11.

4. Hoeper (EX1009) and Morice (EX1010)

M.M. Hoeper, *et al.*, “Combination Therapy with Bosentan and Sildenafil in Idiopathic Pulmonary Arterial Hypertension” (“Hoeper”) is an article published in December 2004 (EX1009; EX1047), and Morice *et al.* (“Morice”) is a comment on Hoeper published in July 2005 (EX1010; EX1048).⁶ Both were published in the European Respiratory Journal, indexed in a library, and available online, and are prior art under pre-AIA §§102(a) and (b).

Neither Hoeper nor Morice was submitted, cited, or considered during prosecution. EX1001, [56]; EX1002, 144-45, 199-201, 233, 317. They were cited in an IDS at the close of reexamination (EX1003, 355-56, 384-85) but were not part of

⁶ Petitioner submits two copies of Morice and Hoeper. Citations to EX1009 and EX1010 apply equally to EX1047 and EX1048, respectively.

the reasons for requesting reexamination (*id.*, 2) or included with the reexamination application (*id.*, 244). The Office has not substantively addressed Hoeper or Morice.

Hoeper teaches the combination of substances having “different mechanisms of action,” including combination therapy using bosentan and sildenafil. EX1009, 1-3. Hoeper explains that “both substances are orally available, act via different mechanisms and are usually well tolerated,” and concludes that the combination of bosentan and sildenafil is safe and effective in patients with idiopathic PAH. *Id.*, 1, 4. When patients treated with bosentan did not exhibit sustained results, adding sildenafil improved their six-minute walk distances and maximum oxygen uptake during cardiopulmonary exercise testing. *Id.*, 3. Hoeper’s combination therapy resulted in significant improvements in exercise capacity, hemodynamic parameters, and better overall clinical health, and was well tolerated by all patients with no major side effects. *Id.*, 2-3.

Submitted as a comment on Hoeper, Morice describes combination treatment with bosentan and tadalafil. EX1010, 1 (noting an “excellent symptomatic response” and maintained reduced pulmonary artery pressure of 61 mmHg, down from 100).

V. GROUNDS ESTABLISHING UNPATENTABILITY

Petitioner requests review of claims 1-57 of the ’847 patent on the grounds listed below which independently render the challenged claims unpatentable as anticipated and/or obvious.

Ground	Reference(s)	35 U.S.C.	Claims
1	Bolli	§102	1-57
2	Bolli and Keyser	§103	1-57
3	Hoeper, Morice, and Bolli	§103	1-57

A. Ground 1: Claims 1-57 Are Anticipated by Bolli

Bolli anticipates each claim for the reasons set forth below. EX1013, ¶¶91-176.

1. Claims 1, 6, & 10

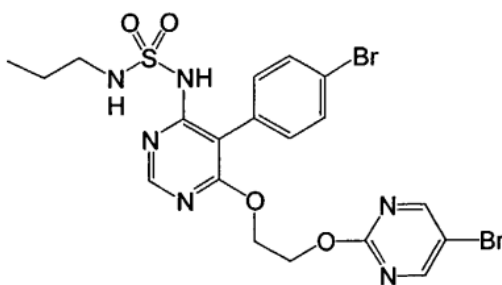
a) Claim 1

(1) “A product containing” [1.Preamble]

Bolli describes “pharmaceutical compositions containing one or more compounds of the general formula I and especially their use as endothelin receptor antagonists.” EX1004, 2. The POSA would have understood a “pharmaceutical composition” as disclosed by Bolli to fall within the plain and ordinary meaning of “product.” EX1013, ¶102.

(2) “the compound of formula (I) below ... in free or pharmaceutically acceptable salt form” [1.1]

Bolli discloses the compound of formula (I)—i.e., macitentan:



EX1004, 29 (right column, first structure); EX1013, ¶¶93, 103-05; EX1004, claim 11. Bolli categorizes macitentan as one of its “especially preferred group of compounds.” EX1004, 22; EX1013, ¶105. Bolli further teaches that macitentan can be in free or pharmaceutically acceptable salt form. EX1004, 13-15; EX1013, ¶106.

(3) *“in combination with at least one compound having PDE5-inhibitory properties, in free or a pharmaceutically acceptable salt form” [1.2]*

Bolli is directed to drug compounds and combinations for treatment of “diseases, which are associated with an increase in vasoconstriction, proliferation or inflammation due to endothelin ... [such as] hypertension, pulmonary hypertension, ... and portal hypertension[, as well as] erectile dysfunction.” EX1004, 12. Bolli explicitly teaches macitentan “in combination with ... vasodilators ... which serve to treat high blood pressure or any cardiac disorders.” *Id.*, 18. In context, including Bolli’s teachings of treatments for, *inter alia*, PH and ED, in combination with the knowledge of this particular field, which includes knowledge of commercially available treatment options, the POSA at the relevant time would have necessarily understood that Bolli’s teaching of macitentan “in combination with ... vasodilators ... which serve to treat high blood pressure or any cardiac disorders” disclosed combining macitentan with sildenafil and tadalafil, both of which are PDE5 inhibitors. EX1013, ¶¶92-99, 109; *VirnetX v. Apple Inc.*, 2023 WL 6933812, *4 (Fed. Cir. 2023).

The POSA knew sildenafil (Viagra®) and tadalafil (Cialis®) were blockbuster “vasodilator” drugs specifically used to treat cardiovascular disorders, as described by Bolli “to treat high blood pressure or any cardiac disorders” EX1004, 18; EX1013, ¶¶96-99; EX1023, 1-2. The POSA would have immediately understood, or at minimum necessarily inferred, that Bolli disclosed macitentan combined with sildenafil and macitentan combined with tadalafil from its explicit teaching to combine macitentan with “vasodilators” to treat vasoconstrictive “cardiac disorders” such as ED, PH, or PAH. EX1004, 18; EX1013, ¶¶96-99, 107-09. Further, because sildenafil and tadalafil were blockbuster drugs, it would have been immediately apparent to the POSA to combine Bolli’s ET antagonist macitentan, which is used for vasoconstrictive diseases, with tadalafil and sildenafil, which are vasodilators with PDE5-inhibitory properties known to be used for vasoconstrictive diseases, *e.g.*, ED and PH. EX1013, ¶36; EX1023, 1-2. Bolli’s description with the POSA’s knowledge was sufficient for the POSA to possess, make, and implement the claimed invention. EX1013, ¶¶92-99, 107-09; *In re Graves*, 69 F.3d 1147, 1152 (Fed. Cir. 1995) (“A reference anticipates a claim if it discloses the claimed invention ‘such that a skilled artisan could take its teachings in **combination with his own knowledge of the particular art and be in possession of the invention.**’”) (emphasis added) (quoting *Application of LeGrice*, 301 F.2d 929, 936 (C.C.P.A. 1962)).

The POSA also knew sildenafil (Viagra®, Revatio®) and tadalafil (Cialis®) were two of a limited class of vasodilators, both well-known and commercially used in the field of cardiovascular medicine. EX1013, ¶¶97; EX1023, 1-4. For example, sildenafil (Viagra®) and tadalafil (Cialis®) were approved by FDA in 1998 and 2003, respectively, for oral administration for ED therapy or treatment. EX1007, 19; EX1008, 26. Widespread use and demonstrated safety and efficacy in treating ED led to the appearance of generic forms of both drugs now on the market. EX1013, ¶¶97. With respect to PH, including PAH, the POSA would have known sildenafil was also approved by FDA in 2005 for PAH treatment under the brand name Revatio®. EX1025. Thus, the POSA would have known sildenafil and tadalafil were disclosed by Bolli’s “vasodilators” since Bolli expressly describes compounds and combinations of macitentan and vasodilators for treating “cardiac disorders” such as ED, hypertension (*e.g.*, PH, PAH), and related diseases involving vasoconstriction. *Id.*, ¶¶92-99, 111.

(4) “for therapeutic use, simultaneously, separately[,] or over a period of time, in the treatment of a disease wherein vasoconstriction is involved” [1.3]

Bolli satisfies this limitation. Bolli’s compounds are for therapeutic use in patients with vasoconstrictive disease. EX1004, 2 (describing “novel pyrimidine-sulfamides ... as active ingredients”). Bolli’s compounds, including macitentan, “mediate[] vasoconstricting and proliferative responses.” *Id.* Additionally, Bolli

discloses that “[e]ndothelin receptor antagonists have demonstrated preclinical and/or clinical efficacy in ... pulmonary and systemic hypertension.” *Id.*, 3, 12 (describing “treatment of diseases, which are associated with an increase in vasoconstriction,” including “hypertension [and] pulmonary hypertension”); *id.*, claims 12, 14, and 18.

The POSA would have understood that treatment with Bolli’s combinations necessarily includes use simultaneously, separately, or over a period of time. EX1013, ¶¶110-17. The ’847 patent defines those terms, and they include use of both drugs “by the same route [of administration] and at the same time,” by different routes at approximately the same time, or where “the entire administration of one of the active ingredients is completed before the administration of the other,” possibly with “one of the active ingredients [administered] for several months before administering the other.” EX1001, 2:14-34. The ’847 patent acknowledges that varied timing of administration was within the POSA’s knowledge and capabilities. *Id.*, 4:7-9 (“[T]he exact administration doses ... will have to be determined by the treating physician.”).

The POSA would have understood that oral macitentan and oral sildenafil (Viagra®) or oral tadalafil (Cialis®)—*i.e.*, their commercially available forms—would have been administered “simultaneously,” *i.e.*, at the same time by the same administration route, including because the drugs are tolerable and for patient

convenience and adherence. EX1013, ¶¶113-14.

The POSA would have also understood that macitentan and sildenafil or tadalafil would have been administered “separately,” *i.e.*, co-administration of an oral PDE5 inhibitor (*e.g.*, sildenafil or tadalafil) and macitentan by any of the routes disclosed by Bolli—rectally, parenterally, sublingually, or via ophthalmic or aerosol preparations—and at approximately the same time. EX1004, 12; EX1013, ¶113.

The POSA would have also understood that macitentan and a PDE5 inhibitor—*e.g.*, sildenafil or tadalafil—would have been administered “over a period of time,” *i.e.*, administration of a first drug for weeks or months, followed by a treatment period with the other drug. EX1013, ¶114. Indeed, “over a period of time” appears to include even treatments separated by months, so long as the patient eventually takes both drugs. *Id.*

The POSA would have understood that Bolli’s combinations are administered simultaneously, separately, and over a period of time.

b) Claim 6

The “pharmaceutical composition” of claim 6 is disclosed by Bolli for the same reasons as the “product” in claim 1. EX1013, ¶¶130-31. Claim 6 recites a “pharmaceutical composition” containing “the compound of formula (I),” *i.e.* macitentan, and “a compound having PDE5-inhibitory properties” as “active principles” along with “at least one excipient.” Bolli discloses a pharmaceutical

composition comprising macitentan and a PDE5 inhibitor. *Supra* §V.A.1; EX1013, ¶¶130-31. Moreover, the POSA would have understood that macitentan and the PDE5 inhibitor could be provided in a single composition for, *e.g.*, convenience and improved patient compliance. EX1013, ¶¶130-31. Bolli further discloses that its pharmaceutical compositions include “at least one excipient.” EX1004, 12 (“The preparations ... can contain ... excipients”); EX1013, ¶130; EX1004, 17-18, claims 12-13, 20.

c) Claim 10

Bolli discloses claim 10 for the same reasons as cited above regarding claims 1 and 6. EX1013, ¶¶136-40.

(1) “A method for the treatment of hypertension or pulmonary hypertension comprising” [10.Preamble]

Bolli discloses that its ET_A antagonists “have demonstrated preclinical and/or clinical efficacy in ... pulmonary and systemic hypertension[.]” EX1004, 3, 12 (teaching that “the described compounds can be used for treatment of diseases [including] hypertension, [and] pulmonary hypertension”); *id.*, claims 12, 14, and 18; EX1013, ¶¶136-37.

(2) “administering to a patient in need thereof an effective amount of a compound of formula (I) as described in claim 1, in free or pharmaceutically acceptable salt form” [10.1]

Bolli discloses administering to a patient the compound of formula (I), macitentan, as explained for claims 1 and 6. *Supra* §§V.A.1.a, V.A.1.b; EX1013,

¶¶93, 136.

(3) *“in combination with at least one compound having PDE5-inhibitory properties, in free or pharmaceutically acceptable salt form” [10.2]*

Bolli discloses macitentan in combination with a PDE5 inhibitor as explained for claims 1 and 6. *Supra* §§V.A.1.a, V.A.1.b; EX1013, ¶¶137-39.

2. Claims 2-4, 7-9, & 11-13

Administration of macitentan with sildenafil or tadalafil satisfies these claims. Claims 2, 7, and 11 recite “the compound having PDE5-inhibitory properties is selected from sildenafil, vardenafil, tadalafil and udenafil.” Claims 3, 8, and 12 specify tadalafil as the PDE5 inhibitor. Claims 4, 9, and 13 specify sildenafil.

The POSA would have understood Bolli to necessarily disclose the product of claim 1, the pharmaceutical composition of claim 6, and the method of claim 10, including combinations of macitentan with sildenafil or tadalafil—compounds used in blockbuster drugs for vasodilation—for the reasons described above regarding claim 1. *Supra* §V.A.1; EX1013, ¶¶95-99, 119, 133, 142; EX1009 (describing the combination of an ET antagonist and sildenafil to treat idiopathic PAH); EX1010, 1 (describing the combination of an ET antagonist and tadalafil for the treatment of PAH). At minimum, the POSA would have inferred combinations of macitentan and sildenafil or tadalafil from Bolli’s disclosure of macitentan, “in combination with ... vasodilators ... which serve to treat high blood pressure or any cardiac disorders”

EX1004, 18; EX1013, ¶¶95-99, 120, 134, 143.

3. Claims 5 & 14-17

Claim 5 recites “the disease wherein vasoconstriction is involved is selected from hypertension, pulmonary hypertension, diabetic arteriopathy, heart failure, erectile dysfunction and angina pectoris.” Claims 14 and 16 specify treatment of PH. Claims 15 and 17 further specify treatment of PAH. Bolli discloses the limitations of claims 5 and 14-17 for the reasons discussed above regarding claims 1, 6, and 10. *Supra* §V.A.1; EX1013, ¶¶121-26, 146-49.

As explained above, Bolli discloses treatments for, *inter alia*, ED, hypertension, and PH, and the POSA would have understood that “vasodilators” includes sildenafil and tadalafil. *Supra* §V.A.1; EX1013, ¶¶124, 148; EX1004, 12 (“[T]he described compounds can be used for treatment of ... hypertension, pulmonary hypertension, [and] erectile dysfunction”).

The POSA would have known PDE5 inhibitors—*e.g.*, sildenafil and tadalafil—were initially developed as treatments for hypertension and PH, among other cardiovascular diseases. EX1013, ¶123; EX1033, 1. The POSA would also have known that numerous publications before the priority date reported sildenafil and tadalafil as known treatments for PH or PAH. EX1013, ¶¶123-24; EX1016, 5, EX1017, 1, EX1018, 1, EX1019, 6, EX1020, 1, EX1021, 2, and EX1022, 1 (describing use of PDE5 inhibitors sildenafil and tadalafil for PH); EX1009, 1

(“[S]everal case series and one small controlled study have suggested that phosphodiesterase-5-inhibitors, such as sildenafil, may have beneficial effects in PAH.”); EX1010, 1 (noting the successful use of tadalafil in combination with bosentan in a patient with PAH). The POSA would also have known sildenafil to be a therapeutic for PAH patients receiving ET antagonists. EX1044, 6 (Figure 1) (“first-line therapy may include oral endothelin receptor antagonists ... [and PDE5] inhibitors should be considered in patients who have failed or are not candidates to other therapies”). Indeed, the POSA would have known the citrate salt of sildenafil was approved to treat PAH in 2005 under the brand name Revatio®. EX1025.

Thus, the POSA would have understood that tadalafil and sildenafil are PDE5 inhibitors and vasodilators that treat hypertension, PH, and PAH.

4. Claims 18 & 38

Claims 18 and 38 require “simultaneous” administration of macitentan and tadalafil (claim 18) or sildenafil (claim 38). Bolli discloses “simultaneous” administration for the reasons described above with respect to claim 1. *Supra* §V.A.1.a.4; EX1013, ¶¶150-51. For example, the POSA would have understood that oral macitentan and oral sildenafil (Viagra®) and tadalafil (Cialis®) (*i.e.*, their commercially available forms) would have been administered at the same time, including because the drugs are tolerable and for patient convenience and adherence. EX1013, ¶¶150-51. Thus, Bolli anticipates claims 18 and 38.

5. Claims 19 & 39

Claims 19 and 39 require “separate” administration of macitentan and tadalafil (claim 19) or sildenafil (claim 39). Bolli discloses “separate” administration for the reasons described above with respect to claim 1. *Supra* §V.A.1.a.4; EX1013, ¶¶152-53. Thus, Bolli anticipates claims 19 and 39.

6. Claims 20-22 & 40-42

Claims 20 and 40 require administration of macitentan and tadalafil (claim 20) or sildenafil (claim 40) “over a period of time.” Bolli discloses administration “over a period of time” for the reasons described above with respect to claim 1. *Supra* §V.A.1.a.4; EX1013, ¶¶154-63.

Claims 21 and 22 recite “the interval between administration of the compound of formula (I) and the administration of tadalafil does not exceed two days” (claim 21) and that interval “does not exceed one day” (claim 22). Claims 41-42 recite sildenafil instead of tadalafil but are otherwise identical to claims 21-22.

The POSA would have understood that the combinations of macitentan and tadalafil or sildenafil would have been administered over a period of time (*i.e.*, at different times). EX1013, ¶¶154-63. For example, morning administration of one drug and evening of the other satisfies the claims, and such administration is well within the knowledge and skill of the POSA, as is clear from Bolli and as acknowledged by PO. EX1001, 4:7-9 (“[T]he exact administration doses ... will

have to be determined by the treating physician.”).

The POSA also would have understood Bolli to disclose treatment with one of these drugs after the patient has already received treatment with the other drug (including treatment months or even years previously). EX1013, ¶¶155, 249, 336. As explained above, macitentan and the PDE5 inhibitor (tadalafil, sildenafil) are both known to be useful in the treatment of vasoconstrictive diseases, including PH and PAH. *Supra* §§V.A.1, V.A.3. For example, the POSA would have understood Bolli to disclose administration of tadalafil or sildenafil alone after a patient did not adequately respond to administration of macitentan alone. EX1013, ¶¶154-63.

Additionally, Bolli discloses daily administration of macitentan. EX1004, 18. The POSA would have known how to dose the commonly prescribed, commercially available tadalafil (Cialis®) and/or sildenafil (Viagra®), including daily doses. EX1013, ¶¶161-63. Administration of daily doses of these drugs would necessarily involve an interval between administrations of less than one day (and thus also less than two days). *Id.*

Thus, Bolli anticipates claims 20-22 and 40-42.

7. Claims 23-37 & 43-57

Claims 23-37 and 43-57 depend from various other claims addressed above but all recite limitations regarding macitentan and either tadalafil (claims 23-37) or sildenafil (claims 43-57) doses. The POSA would have understood Bolli to also

anticipate these claims.

Macitentan doses. Claims 23, 26, 29, 32, 35, 43, 46, 49, 52, and 55 recite a macitentan dose of 0.05mg to 2mg per kilogram of patient body weight (abbreviated hereinafter as “mg/kg”). Claims 25, 28, 31, 34, 37, 45, 48, 51, 54, and 57 recite a narrower range of 0.1mg/kg to 1mg/kg.

Bolli discloses “dosages of 0.1-50 mg/kg body weight per day,” which overlaps the claimed range of 0.05mg/kg to 2mg/kg and fully encompasses the claimed range of 0.1mg/kg to 1mg/kg. EX1004, 12; EX1013, ¶165.

The additional macitentan dosage limitations of claims 43, 45-46, 48-49, 51-52, 54-55, and 57 are identical to the additional limitations of claims 23, 25-26, 28-29, 31-32, 34-35 and 37, respectively.⁷ Hence, these limitations are anticipated by Bolli for the same reasons. EX1013, ¶165.

Tadalafil doses. Claims 24, 27, 30, 33, and 36 recite a tadalafil dose of 0.01mg/kg to 1mg/kg. The label for FDA-approved Cialis®—tadalafil—describes oral tablets in 5mg, 10mg, or 20mg dosages. EX1008, 2; EX1013, ¶¶167-70. Assuming a standard 70kg mass for an average patient, the 5mg and 20mg dosages

⁷ Claims 43, 45-46, 48-49, 51-52, 54-55, and 57 depend from claims specifying sildenafil as the PDE5 inhibitor; claims 23, 25-26, 28-29, 31-32, 34-35 and 37 depend from claims specifying tadalafil.

equate to a dose range of 0.07mg/kg to 0.29mg/kg. EX1013, ¶¶167-70. Thus, administration of those 5mg, 10mg, and 20mg dosages encompass or overlap the ranges of claims 24, 27, 30, 33, and 36. *Id.*

Sildenafil doses. Claims 44, 47, 50, 53, and 56 recite that sildenafil is administered in a dose of 0.1mg/kg to 2mg/kg. The label for FDA-approved Viagra®—sildenafil—describes oral tablets available in 25mg, 50mg, or 100mg sildenafil dosages. EX1007, 1; EX1013, ¶¶171-73. Assuming a standard 70kg mass for an average patient, the 25-100mg dosages equate to a dose range of 0.36-1.43mg/kg. Thus, those 25mg, 50mg, and 100mg dosages encompass or overlap the ranges of claims 44, 47, 50, 53, and 56. Likewise, Revatio® oral tablets are available in 20mg sildenafil dosages. EX1025, 1. Again, assuming a 70kg patient, this equates to a 0.29mg/kg dosage. EX1013, ¶¶172-73.

In any event, these claims define dosages for all three compounds in terms of patient body weight. As the '847 patent recognizes, the POSA would have understood how to arrive at “the exact administration doses.” EX1001, 4:7-9. Indeed, doses “will ***have to be*** determined by the treating physician”—*i.e.*, on a patient-by-patient basis, taking into account factors such as medical history and the like. *Id.* (emphasis added). Thus, doses within the claimed ranges would have been immediately apparent to the POSA. EX1013, ¶¶164-76.

B. Ground 2: Claims 1-57 Are Obvious Over Bolli in View of Keyser

1. Claims 1, 6, & 10

a) Claim 1

(1) “A product containing” [1.Preamble]

Bolli teaches or renders obvious a product. *Supra* §V.A.1.a.1; EX1013, ¶193.

Keyser also teaches a product. For example, it claims pharmaceutical compositions comprising an ET_A antagonist, a PDE5 inhibitor and a pharmaceutical carrier. EX1005, claims 34-43, [002] (disclosing “combination therapies” and “pharmaceutical compositions”); EX1013, ¶194.

(2) “the compound of formula (I) below ... in free or pharmaceutically acceptable salt form” [1.1]

As explained above, Bolli teaches “the compound of formula (I)” (macitentan) in free or pharmaceutically acceptable salt form. *Supra* §V.A.1.a.2; EX1013, ¶195. Keyser further teaches that the PDE5 inhibitor and ET_A antagonists used in its combinations can be in free or pharmaceutically acceptable salt form. EX1005, [073].

(3) “in combination with at least one compound having PDE5-inhibitory properties, in free or a pharmaceutically acceptable salt form” [1.2]

As explained above, Bolli teaches or renders obvious that macitentan may be used in combination with vasodilators having PDE5-inhibitory properties, and the POSA would have understood Bolli as disclosing the combination of macitentan

with vasodilators sildenafil or tadalafil. *Supra* §V.A.1.a.3; EX1013, ¶196. Even if PO argues to the contrary, it would have been obvious to use sildenafil or tadalafil—the active ingredients in blockbuster drugs Viagra® and Cialis®—as the vasodilators in combination with macitentan, as taught by Bolli. *Id.*, ¶187.

The POSA would have turned to Keyser from Bolli’s teachings of macitentan in combination with one or more vasodilators—which the POSA knew to include PDE5 inhibitors as explained above in §V.A.1.3—because Keyser is specifically directed to combinations of ET antagonists and PDE5 inhibitors, is in the same field, is directed to the same problem, and proposes to treat the same types of diseases as Bolli’s combinations (*e.g.*, ED, PH, PAH). EX1005, [002], [030]-[031]; EX1013, ¶197. Keyser teaches that useful PDE5 inhibitors include, “*e.g.*, ... tadalafil (CIALIS) ... and sildenafil.” EX1005, [046]; EX1013, ¶197. Keyser also teaches that “other forms of the PDE5 inhibitor, such as ... salts and complexes thereof, may also be used.” EX1005, [046], [073]. Thus, Keyser teaches that the PDE5 inhibitor can be in free or pharmaceutically acceptable salt form.

As the Examiner found, the POSA had ample reasons to combine macitentan with a PDE5 inhibitor with a reasonable expectation of success. EX1013, ¶¶189, 199-201; EX1002, 222-24. For example, Keyser expressly says to combine an ET_A (as taught by Bolli) with a PDE5 inhibitor. Keyser reasons that “it would be beneficial to combine a PDE5 inhibitor with an ET_A antagonist to provide

complimentary treatment and reduce dosage amounts and/or side effects related to treatment with PDE5 inhibitors.” EX1005, [045]. As Keyser teaches, the combination will provide “complementary” treatment. The POSA would have understood that complementary treatments using two different pathways, such as an ET_A and PDE5 inhibitor, may result in synergistic effect. EX1013, ¶¶199-201. Indeed, Keyser teaches that the combinations “reduce dosage amounts and/or side effects.” EX1005, [045]. Keyser teaches PDE5 inhibitors generally and also specifically identifies sildenafil, tadalafil, and vardenafil. *Id.*, [046], [029].

Bolli and Keyser are also in the same field of art regarding the treatment of vasoconstrictive diseases, including ED, PH, and PAH. And they both teach combination therapies involving ET_A antagonists and vasodilators (*e.g.*, PDE5 inhibitors). The POSA knew the advantages of treating a disease or condition with two or more active ingredients targeting different biological pathways, including that doing so may be more effective than either drug alone or even more than the additive effects of the drugs administered separately. EX1013, ¶¶200-02. The POSA, therefore, would have been motivated to combine the PDE5 inhibitors, such as sildenafil or tadalafil, used in the combination therapies in Keyser with the macitentan-vasodilator combinations therapies in Bolli. *Id.*, ¶¶180-82, 196-203.

The POSA would have made that combination with a reasonable expectation of success. *Id.*, ¶¶189, 201-03. Bolli teaches that macitentan is an effective drug for

treating vasoconstrictive diseases. *Id.*, ¶¶44, 196, 202. Keyser likewise teaches that ET_A antagonists are effective, and so were PDE5 inhibitors. *Id.*, ¶203. Keyser's Example 1 describes the results of a study of healthy volunteers showing administration of sitaxsentan—an ET_A antagonist—and sildenafil did not have an overall impact on pharmacokinetics. *Id.*; EX1005, [093]-[097]. Keyser also describes an efficacy study involving “[m]inimal drug interaction and side effects ... while maintaining successful therapeutic effect.” EX1005, [098]-[0100]. The POSA also knew that these classes of drugs were effective and knew that combination therapies have at minimum the potential to provide a combined effect that exceeds their efficacy individually. EX1013, ¶203; *infra* §V.B.8.b. Based on Bolli and Keyser, in view of the POSA's background knowledge, the POSA would have expected the combination of macitentan and a PDE5 inhibitor such as tadalafil or sildenafil to be a safe and effective treatment for a disease associated with vasoconstriction. EX1013, ¶¶197-204.

(4) “for therapeutic use, simultaneously, separately over a period of time, in the treatment of a disease wherein vasoconstriction is involved” [1.3]

Bolli and Keyser teach therapeutic use of an ET_A antagonist (*e.g.*, macitentan) and at least one compound having PDE5-inhibitory properties, simultaneously, separately, or over a period of time, in the treatment of a disease wherein vasoconstriction is involved. EX1013, ¶¶204-07; *cf. Loctite Corp. v. Ultraseal Ltd.*,

781 F.2d 861, 868 (Fed. Cir. 1985).

Bolli teaches administration for therapeutic use in the treatment of a disease wherein vasoconstriction is involved for the reasons cited above. *Supra* §V.A.1.a.4. Keyser teaches that its combinations are “useful for the treatment and/or prevention of cardiac disorders such as [PAH].” EX1005, [002]. Keyser discloses the vascular condition treated as being “selected from the group consisting of erectile dysfunction, atherosclerosis, renal failure, hypertension, congestive heart failure, diabetic nephropathy, diabetic neuropathy, interstitial lung disease, obstructive sleep dyspnea, obstructive sleep apnea and resistant hypertension”—*i.e.*, diseases involving vasoconstriction. *Id.*, claim 15, [030], [031], [069].

The POSA further understood that Bolli and Keyser’s combinations include administration simultaneously, separately, or over a period of time, and that such use would have been obvious. EX1013, ¶¶204-07. The POSA would have understood these treatment timing limitations based on Bolli for the reasons described above. *Supra* §V.A.1.a.4.

Keyser states that its combinations can be administered with “dual drug tablets comprising both an ET_A antagonist and a PDE5 inhibitor.” EX1005, [032]. Thus, it was obvious that the combination of an ET_A antagonist and PDE5 inhibitor, such as macitentan and sildenafil or tadalafil, could therefore be administered in one dual-drug dosage form, which is an example of “simultaneous” administration. EX1013,

¶206. “However, the two drugs may [also] be provided in separate dosage formulations so that each may be administered substantially concurrently or at [*sic*] sequentially to provide required therapeutic amounts.” EX1005, [032]. Keyser also recognizes that drugs may be administered using different routes of administration. *Id.*, [070] (referring to dosage variation “depending upon the dosage form employed, and the route of administration utilized”). In addition, Keyser states that “[d]osage amount *and interval* can be adjusted[.]” *Id.*, [071] (emphasis added). Keyser therefore teaches varying the number of drugs in the dosage form(s) used, the routes of administration, types of dosage forms, and timing of dosing (same time, “substantially concurrently,” and “sequentially”).

Thus, it was also obvious that the combination of macitentan and a PDE5 inhibitor, such as tadalafil and sildenafil, could be administered simultaneously in the same dosage form, simultaneously in separate dosage forms, at approximately the same time using different dosage forms and routes of administration, or sequentially (with varying “interval[s]”) using different routes of administration. Treatment “simultaneously, separately[,], over a period of time” was obvious. EX1013, ¶¶204-07.

b) Claim 6

The “pharmaceutical composition” of claim 6 is obvious over Bolli and Keyser for the same reasons as the “product” of claim 1. *Supra* §V.B.1.a.1; EX1013,

¶¶215-17. Claim 6 recites a “pharmaceutical composition” containing macitentan and a PDE5 inhibitor as “active principles” along with “at least one excipient.” As described above with respect to claim 1, Bolli discloses a pharmaceutical composition comprising macitentan and a PDE5 inhibitor along with an excipient, and use of excipients in pharmaceuticals is well known. *Supra* §V.A.1.b; EX1013, ¶215.

Keyser also teaches pharmaceutical compositions comprising at least one excipient. EX1013, ¶217; EX1005, [079]-[080] (teaching excipients for controlled release formulations and solid dosage forms).

Thus, it would be obvious to use the combination of macitentan and a PDE5 inhibitor along with an excipient.

Accordingly, pharmaceutical compositions comprising macitentan, a PDE5 inhibitor, and at least one excipient are obvious over Bolli and Keyser (as well as the common knowledge of the POSA). EX1013, ¶¶215-17.

c) Claim 10

(1) “A method for the treatment of hypertension or pulmonary hypertension comprising” [10.Preamble]

As explained above, Bolli teaches a method for the treatment of hypertension or PH. *Supra* §V.A.1.c.1; EX1013, ¶225.

Likewise, Keyser claims “[a] method of treating pulmonary hypertension comprising administering to a subject in need thereof an effective amount of a) a

phosphodiesterase 5 (PDE5) inhibitor and b) an endothelin A receptor (ET_A) antagonist.” EX1005, claim 1; *id.*, [030], [031], [069]; *id.*, claim 15 (defining the vascular condition treated by the claimed method as “selected from the group consisting of erectile dysfunction, ... hypertension, ... and resistant hypertension”); EX1013, ¶¶225-26. Keyser also describes its combination therapies and pharmaceutical compositions comprising ET_A antagonists and PDE5 inhibitors as “useful for the treatment and/or prevention of cardiac disorders such as [PAH].” EX1005, [002].

(2) *“administering to a patient in need thereof an effective amount of a compound of formula (I) as described in claim 1, in free or pharmaceutically acceptable salt form” [10.1]*

As discussed above, Bolli teaches the use of macitentan in an effective amount. Thus, this limitation is obvious for the reasons discussed above. *Supra* §§V.A.1.c.2, V.B.1.a, V.B.1.b; EX1013, ¶224.

(3) *“in combination with at least one compound having PDE5-inhibitory properties, in free or pharmaceutically acceptable salt form” [10.2]*

As discussed above, Bolli teaches using macitentan in combination with vasodilators, which the POSA would have understood discloses sildenafil and tadalafil, and Keyser expressly teaches using a PDE5 inhibitor with an ET_A antagonist, including sildenafil and tadalafil. *Supra* §V.B.1.a. Thus, this limitation is obvious. EX1013, ¶¶224-27.

2. Claims 2-4, 7-9, & 11-13

Claims 2, 7, and 11 recite “the compound having PDE5-inhibitory properties is selected from sildenafil, vardenafil, tadalafil and udenafil.” Claims 3, 8, and 12 specify tadalafil as the PDE5 inhibitor and claims 4, 9, and 13 specify sildenafil.

As explained above, the obvious combination of Bolli and Keyser includes macitentan and PDE5 inhibitors. *Supra* §V.B.1; EX1013, ¶¶209-11, 219-20, 229. Keyser specifically teaches that the PDE5 inhibitor in its combinations with an ET_A antagonist can be sildenafil, tadalafil, or vardenafil, among others. EX1005, [046]; *id.*, claims 9 and 11-14; EX1013, ¶¶209-11.

Thus, the combination of Bolli and Keyser disclose using macitentan with sildenafil or tadalafil, which renders claims 2-4, 7-9, and 11-13 obvious. EX1013, ¶¶209-11, 219-20, 229.

3. Claims 5 & 14-17

Claim 5 recites that the therapeutic use is for at least one of a list of certain vasoconstrictive diseases, including PH and ED. Claims 14 and 16 specify treatment of PH and claims 15 and 17 further specify treatment of PAH.

Bolli teaches treatment of vasoconstrictive diseases, including “pulmonary hypertension.” EX1004, 3, 12, claims 12, 14, and 18; *supra* §§V.A.1.c.1, V.A.3. Keyser expressly teaches treating “cardiac disorders such as [PAH].” EX1005, [002]. Bolli and Keyser teach treatment of PH and PAH, rendering obvious the

limitations of claims 5 and 14-17. *Supra* §§V.A.1.a.4, V.A.1.c.1, V.A.3, V.B.1.c.1; EX1013, ¶¶213, 231-32.

4. Claims 18 & 38

Claims 18 and 38 require “simultaneous” administration of macitentan and tadalafil (claim 18) or sildenafil (claim 38) (*i.e.*, by the same administration route and at the same time). EX1001, 2:15-19.

As explained above, Bolli teaches macitentan is suitable for oral administration. *Supra* §§V.A.1.a.4, V.A.4, V.B.1.a.4; EX1004, 12; EX1013, ¶¶235-36.

As explained above, Keyser also teaches that ET_A antagonists and tadalafil can be provided in a dual dosage form (*i.e.*, simultaneously) or in separate dosage forms “substantially concurrently” or “sequentially.” EX1005, [032], [025]; EX1013, ¶237. A dual dosage form would provide both drugs at the same time using the same administration route (“simultaneously”). *Supra* §§V.A.1.a.4, V.A.4, V.B.1.a.4; EX1013, ¶237. Claims 18 and 38 are therefore obvious over Bolli and Keyser.

5. Claims 19 & 39

Claims 19 and 39 require “separate” administration of macitentan and tadalafil (claim 19) or sildenafil (claim 39) (*i.e.*, at approximately the same time by at least two different routes). EX1001, 2:20-24.

As explained above, Bolli teaches that macitentan can be administered orally, parenterally, sublingually, by inhalation, and by other routes. *Supra* §§V.A.1.a.4, V.A.5, V.B.1.a.4; EX1004, 12; EX1013, ¶243.

Keyser teaches either ET_A antagonists and/or the PDE5 inhibitor (tadalafil or sildenafil) may be administered orally or by other routes. EX1005, [080]-[089] (describing oral dosage forms), and [090] (describing compositions to be administered to the respiratory tract); EX1013, ¶244.

Further, as explained above, Keyser teaches administration of combinations of ET_A antagonists and PDE5 inhibitors (*e.g.*, tadalafil or sildenafil) in separate dosage forms “substantially concurrently” or “sequentially” and with varying time intervals between. EX1005, [025], [032], [071]; EX1013, ¶244. Keyser explains “sequentially [includes] variations such as every other day treatment of agent and daily or multiple daily administrations of the other agent as required to achieve therapeutic effect. The combination therapy may be accomplished by providing the PDE5 inhibitor and the ET_A antagonist in separate dosage forms packaged together with instructions for the dosage administration regimen.” EX1005, [072]; EX1013, ¶244.

The POSA was also familiar with different routes of administration and the ability to vary the interval between administrations. EX1013, ¶¶243-44. Thus, separate administration of the claimed combinations was obvious over Bolli and

Keyser. EX1013, ¶¶240-46.

6. Claims 20-22 & 40-42

Claims 20 and 40 require administration of macitentan and tadalafil (claim 20) or sildenafil (claim 40) “over a period of time” (*i.e.*, at different times). EX1001, 2:25-35.

Claims 21 and 22 recite “the interval between administration of the compound of formula (I) and the administration of tadalafil does not exceed two days” (claim 21) and that said interval “does not exceed one day” (claim 22).

Claims 41-42 recite sildenafil instead of tadalafil but are otherwise identical to claims 21-22.

As described above, the POSA would have understood that administration over a period of time with intervals of less than two days or less than one day could be performed from Bolli alone, and it was also within the POSA’s knowledge and skill. *Supra* §§V.A.1.a.4, V.A.6; EX1013, ¶¶247-53. For example, morning administration of one drug and evening of the other would satisfy the claims, rendering them obvious. EX1013, ¶248.

Additionally, Keyser teaches varying the administration route and the “interval” between drugs. *Supra* §§V.B.1.a.4, V.B.5; EX1005, [071] (“The exact formulation, route of administration, and dosage is determined by an individual physician in view of the patient’s condition. Dosage amount *and interval* can be

adjusted individually to provide levels of the active agents that are sufficient to maintain therapeutic or prophylactic effects.”) (emphasis added). And Keyser explains that the PDE5 inhibitor and ET_A antagonist can be administered “sequentially in either order,” (EX1005, [025]) and that “sequentially is meant to include variations such as every other day treatment[,]” (*id.*, [072]). From these disclosures, not to mention the POSA’s knowledge and skill, it would have been obvious to administer the combination of macitentan and a PDE5 inhibitor (*e.g.*, sildenafil or tadalafil) on an every-other-day basis, which renders claims 20-22 and 40-42 obvious. EX1013, ¶249. Further, treatment with one of these drugs after they have already received treatment with the other (even including treatment months previously) would also have been obvious to the POSA since, as explained above, macitentan and the PDE5 inhibitor (tadalafil, sildenafil) are both known to be useful in the treatment of vasoconstrictive diseases, including PH and PAH. *Supra* §V.B.1.c.1, EX1013, ¶249. For example, the POSA would have found it obvious to administer tadalafil or sildenafil alone after a patient did not adequately respond to administration of macitentan alone, or vice versa. EX1013, ¶249.

It would therefore have been obvious to the POSA to administer macitentan and tadalafil over a period of time where the interval is less than two days or less than one day.

7. Claims 23-37 & 43-57

Claims 23-37 and 43-57 depend from various other claims but all recite limitations regarding macitentan and either tadalafil (claims 23-37) or sildenafil (claims 43-57) doses. These claims are obvious over Bolli and Keyser.

Macitentan doses. Claims 23, 26, 29, 32, and 35 recite a dose range for macitentan of 0.05mg/kg to 2mg/kg. Claims 25, 28, 31, 34, and 37 narrow this range to 0.1mg/kg to 1mg/kg. As explained above, Bolli teaches the macitentan dosage ranges recited in these claims. *Supra* §V.A.7; EX1013, ¶260. Additionally, Keyser teaches “[d]aily amounts for ET_A antagonists will be in the range of 5 mg to 125 mg.” EX1005, [074]; EX1013, ¶261. Assuming a standard 70kg mass for an average patient, the 5mg and 125mg amounts equate to a dose range of 0.07mg/kg to 1.8mg/kg. Thus, Keyser’s disclosed range—like Bolli’s—encompasses or overlaps the ranges of these claims, rendering them obvious. EX1013, ¶¶259-62.

The additional macitentan dosage limitations of claims 43, 45-46, 48-49, 51-52, 54-55, and 57 are identical to the additional limitations of claims 23, 25-26, 28-29, 31-32, 34-35 and 37, respectively.⁸ Hence, these limitations are obvious over Bolli in view of Keyser for the same reasons. *Id.*, ¶¶260-63.

Tadalafil doses. Claims 24, 27, 30, 33, and 36 recite a dose range for tadalafil

⁸ See *supra*, n.7.

of 0.01mg/kg to 1mg/kg. The doses are obvious for the reasons discussed above regarding Ground 1. *Supra* §V.A.7. In addition, Keyser teaches “[d]aily amounts for PDE5 inhibitors will be in the range of 50 mg to 250 mg.” EX1005, [074]. Keyser’s disclosed range encompasses or overlaps the ranges of claims 24, 27, 30, 33, and 36. For example, administering 50mg to a 70kg patient equates to 0.71mg/kg. EX1013, ¶¶263-65.

Sildenafil doses. Claims 44, 47, 50, 53, and 56 recite that sildenafil is administered in a dose of 0.1mg/kg to 2mg/kg. The doses are obvious for the reasons discussed above regarding Ground 1. *Supra* §V.A.7. In addition, Keyser teaches “[d]aily amounts for PDE5 inhibitors will be in the range of 50 mg to 250 mg.” EX1005, [074]. Keyser’s disclosed range encompasses or overlaps the ranges of claims 44, 47, 50, 53, and 56. For example, administering 50mg to a 70kg patient equates to 0.71mg/kg. EX1013, ¶¶263-65.

Accordingly, claims 23-37 and 43-57 are obvious over Bolli and Keyser. EX1013, ¶¶259-65.

8. No secondary considerations render any of claims 1-57 non-obvious

There are no secondary considerations that support nonobviousness of the challenged claims. PO has asserted that the claims are supported by “surprising

results,”⁹ arguing that (1) Keyser’s combinations are limited to ET antagonist compounds that are “selective” for ET_A as an “explicit ... requirement” and (2) post-priority (not prior art) references show that macitentan is a “dual” receptor antagonist, such that Keyser taught away. EX1006, 385-86. These arguments are flawed, as explained below.

a) The alleged unexpected results are not commensurate with the claims, nullifying any indicia of non-obviousness

The ’847 patent asserts, as PO did during prosecution, that the claimed combinations provide an “unexpected synergistic effect.” EX1001, 1:62-63. Unexpected results must be “commensurate” with the scope of the claims. *E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1011-12 (Fed. Cir. 2018) (holding testing of only a single pressure of 4.2 bars did not establish unexpected results across a range of 1-10 bars). Unexpected results do not support nonobviousness when their scope is “plainly disproportionate to the scope of the claim.” *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1308 (Fed. Cir. 2011).

⁹ Patent Owner has not asserted any other secondary considerations in prosecution of the ’847 patent or the ’148 Application, and Patent Owner does not believe any support nonobviousness. If Patent Owner submits evidence of any other secondary consideration, Petitioner reserves the right to respond with argument and evidence.

Here, the only support for the alleged synergistic effect is Examples 1-3, which are limited to data on the “acute effects” (one-time dose) of macitentan alone and combined with tadalafil or sildenafil when administered by “oral gavage” to unknown numbers of two types of rats. EX1001, 5:15-6:9, 6:52-7:19. The patent does not describe any testing in humans or any other species, and it appears that if a rat was given both macitentan and sildenafil/tadalafil, those drugs were given “simultaneously” (same administration route at the same time).

The Examples barely touch the scope of the claims. Claim 1 purports to cover any combination of macitentan with *any* PDE5 inhibitor given at almost *any* time relative to one another: simultaneously, separately, or “over a period of time,” including where “one of the active ingredients [is administered] for several months before administering the other active ingredient or ingredients” with “no simultaneous administration.” *Id.*, 2:25-35. The ’847 patent claims are “plainly disproportionate.” *Genetics Inst.*, 655 F.3d at 1308. For example:

The claims include:	But the Examples describe only:
Chronic dosing (all claims)	Single administration
Any species (all claims)	Rats only

The claims include:	But the Examples describe only:
Any PDE5 inhibitor (claims 1, 5, 6, 10)	Tadalafil or sildenafil only
Vardenafil as the PDE5 inhibitor (claims 1-2, 5-7, 10-11)	No disclosure
Udenafil as the PDE5 inhibitor (claims 1-2, 5-7, 10-11)	No disclosure
Any administration timing (claims 1-17, 23-25, 43-45)	One-time, simultaneous dosing of macitentan with tadalafil/sildenafil
Separate dosing (claims 1-17, 19, 23-25, 43-45)	No disclosure
Over a period of time dosing (claims 1-17, 20-25, 29-37, 43-45)	No disclosure
Any dose of macitentan (claims 1-22)	0.3mg/kg
Any dose of macitentan within 0.05- 2mg/kg (claims 23-24, 26-27, 29-30, 32-33, 35- 36, 43-44, 46-47, 49-50, 52-53, 55-56)	0.3mg/kg

The claims include:	But the Examples describe only:
Any dose of macitentan within 0.1-1mg/kg (claims 25, 28, 31, 34, 37, 45, 48, 51, 54, 57)	0.3mg/kg
Any dose of tadalafil (claims 1-3, 5-8, 10-12, 14-15, 18-23, 25-26, 28-29, 31-32, 34-35, 37)	10mg/kg
Any dose of tadalafil within 0.01-1mg/kg (claims 24, 27, 30, 33, 36)	10mg/kg
Any dose of sildenafil (claims 1-2, 4-7, 9-11, 13, 16-17, 38-43, 45-46, 48-49, 51-52, 54-55, 57)	30mg/kg
Any dose of sildenafil within 0.1-2mg/kg (claims 44, 47, 50, 53, 56)	30 mg/kg
Any disease wherein vasoconstriction is involved	Dahl-sensitive rats that develop hypertension upon salt intake and

The claims include:	But the Examples describe only:
(claims 1-4, 6-9)	spontaneously hypertensive rats
Administration of any additional compounds along with macitentan and one PDE5 inhibitor (all claims)	No additional compounds

Compare EX1001, claims 1-57 *with* Examples 1-3; EX1013, ¶¶399-409.

Unexpected results cannot support the breadth of these claims given the specification’s extremely narrow and disproportionate disclosure. *Genetics Inst.*, 655 F.3d at 1308 (explaining the holding in *Peterson* as “affirming obviousness where the applicant claimed an alloy with 1-3% rhenium, yet presented unexpected results only for 2% rhenium, and evidence suggested that 3% rhenium possessed inferior properties” (citing *In re Peterson*, 315 F.3d 1325, 1331 (Fed. Cir. 2003))).

The Office never previously considered whether the claims and unexpected results were commensurate as required by law. As is clear, they are not even close.

b) The POSA would have expected complementary results from a macitentan-PDE5 combination

PO’s “unexpected” results argument also fails because the results are not actually unexpected or surprising. The POSA would have expected combining an endothelin antagonist and PDE5 inhibitor to have beneficial, complementary results.

Keyser expressly teaches that its combinations “will act in a *complimentary fashion* for the multiple pathways ... *to provide superior efficacy* and/or dosage regimes and/or reduction side effects.” EX1006, 384 (citing EX1005, [067]) (emphases added); EX1013, ¶¶46, 180, 199. Bolli likewise teaches combining macitentan with “vasodilators.” EX1004, 18. Hoeper describes how, when a monotherapy of bosentan—a dual antagonist—did not work, adding sildenafil provided significant improvements in exercise capacity, hemodynamics, and overall health. EX1009, 2-3; EX1014, 4-6. Morice describes how bosentan combined with sildenafil caused exercise tolerance to “double[,],” and changing to tadalafil had an “excellent symptomatic response” while maintaining reduced pulmonary arterial pressure. EX1010, 1. The POSA would understand that “the combination of different drugs with different mechanisms of action and different ways of metabolism is an attractive therapeutic option with the hope of maximizing effectiveness[.]” EX1014, 2.

The prior art therefore includes several arrows all pointing in the direction of using the different mechanisms of actions of ET antagonists and PDE5 inhibitors together to achieve complementary action and superior results. EX1013, ¶¶375-98.

Thus, the POSA would not have been surprised that two drugs acting on different biological pathways would result in a supra-additive or “synergistic” reduction in blood pressure or other symptoms of vasoconstrictive diseases.

EX1013, ¶¶376-97. For example, the POSA knew that endothelin antagonism removes one of the most potent vasoconstrictors from exerting its effects on blood vessels, and that enhancement of endogenous nitric oxide by PDE5 inhibition provides enhanced levels of cGMP, one of the most potent blood vessel vasodilators. *Id.*, ¶381. The POSA further understood that combining an ET antagonist with a PDE5 inhibitor achieves dual antagonism of ET-1 receptors on smooth muscle cells from airways and blood vessels resulting in concomitant enhanced airflow and blood flow. *Id.*, ¶¶382-84. For example, the POSA knew that prevention of airway smooth muscle cell contraction, like vascular smooth muscle cell contraction, leads to vasodilation of bronchial and blood vessel smooth muscle, respectively, such that airflow and blood flow both increase. *Id.*, ¶¶384-97.

Indeed, the potential for synergy is one of the reasons that combinations are considered in drug development. *Id.*, ¶¶37-38, 377-97. The POSA knew that combining drugs having different mechanisms of action or which act on different biological pathways is a common sense way to maximize an intended therapeutic effect, especially where the disease to be treated involves the interplay of different systems, such as the respiratory and circulatory systems. *Id.*, ¶¶37, 387. And, where drugs work via different mechanisms to achieve the same endpoint—*e.g.*, an endothelin antagonist and a PDE5 inhibitor—the POSA would expect the combination of such drugs to exhibit synergy. *Id.*, ¶394.

Thus, the POSA would have expected pharmacological synergy. PO and the Office both failed to consider and compare to the “complementary” benefits Keyser teaches. *Supra* §V.B.8.b. The alleged results are not surprising and therefore do not weigh in favor of nonobviousness.

Even if the results were surprising—they are not—PO’s attempt to overcome *prima facie* obviousness by asserting unexpected results is foreclosed by law because the purported invention is at best a latent property of what was well known. In *In re Baxter Travenol Labs.*, the court considered nonobviousness of a “blood bag system” where the bag used a DEHP plasticizer that, it was claimed, unexpectedly prevented hemolysis. 952 F.2d 388, 392 (Fed. Cir. 1991). The court found no unexpected results because “[m]ere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention.” *Id.*

c) PO’s post-priority references do not support assertion of manufactured “surprising” results

PO’s and the Office’s reliance on post-priority references, Iglarz and Bolli 2012, was error. EX1002, 205-06, 238-39; EX1006, 345-46. To rebut a *prima facie* case of obviousness, “the results must be ‘unexpected by one of ordinary skill in the art *at the time of [the] application,*’” *Forest Labs, LLC*, 918 F.3d at 937 (emphasis added) (quoting *In re Geisler*, 116 F.3d at 1470).

Iglarz was published in 2008 and Bolli 2012 was published in 2012, both well after the earliest claimed priority date (August 29, 2006). In certain circumstances,

post-priority evidence can be considered. Here, however, the post-priority references are not used to provide data showing “unexpected results” for the combination of macitentan with a PDE5 inhibitor; the limited data PO relies on for that purpose is in the ’847 specification. EX1001, 6:52-7:19 (Examples 1-3). Rather, post-priority Iglarz and Bolli are cited to impermissibly supplement information the POSA would understand at the time of the invention to redefine a known compound’s selectivity. This litigation-inspired fiction cannot support nonobviousness, as the POSA “would not have been aware” of the cited characteristics and therefore “could not have been surprised.” *Forest Labs*, 918 F.3d at 937 (finding error in district court unexpected results analysis based upon post-priority evidence of toxicity for other routes of administration).

Because Iglarz and Bolli do not provide evidence of unexpected results, they cannot be considered. And without Iglarz and Bolli 2012, there is no basis to conclude that the POSA would have believed macitentan to be a dual receptor antagonist, fatally undermining PO’s previous arguments regarding unexpected results.

d) Even if considered, post-priority Iglarz and Bolli 2012 do not support surprising results

(1) PO misapplies Iglarz’s “in vivo” data based on Keyser’s “in vitro” selectivity preference

When viewed against Keyser’s *in vitro* selectivity teaching, the POSA would

understand Iglarz's *in vitro* data to **confirm** macitentan's ET_A selectivity. PO, however, ignores that apples-to-apples, *in vitro*-to-*in vitro*, comparison. Instead, it misapplies Iglarz's "*in vivo*" data to (mistakenly) argue that the POSA would be surprised by macitentan's results because *in vivo* selectivity was lower than *in vitro* selectivity. EX1006, 385-86. PO is wrong.

Keyser's teaching that "in general" the ET_A antagonist should have a selectivity ratio of 100 or more is based upon *in vitro* data. EX1005, [048] (referring to "*in vitro* assays"), [049] (same), [059] (describing relative binding ratio of at least 100), [060] (referring to "*in vitro* receptor affinity ratio"). The POSA would understand that macitentan exceeded an ET_A:ET_B selectivity ratio of 100 based on Bolli *and* PO's post-priority references. First, Bolli's Example 104 is a homolog of macitentan differing structurally by only a single carbon atom. EX1013, ¶¶44, 359-67. Based on *in vitro* data, Example 104 has an ET_A IC₅₀ of 0.88 nM and a substantially greater ET_B IC₅₀ of 601 nM, which yields an ET_A:ET_B selectivity ratio of 683. EX1013, ¶¶44, 365; EX1004, 7. The POSA would have expected macitentan to have the same or substantially the same properties as Bolli's Example 104. EX1013, ¶¶364-67. Second, Iglarz discloses a selectivity ratio for macitentan of 782 in favor of ET_A. EX1006, 385; EX1011, 6 (describing an IC₅₀ of 0.5 for ET_A and 391 for ET_B); EX1013, ¶368.

Both Bolli's (683) and Iglarz's (782) ET_A:ET_B selectivity ratio far exceed

Keyser’s preference for a selectivity ratio of 100 or more. As a result, neither Bolli nor Iglarz would cause the POSA to be surprised by the alleged synergistic effects. *Cf.* EX1003, 229-30.

(2) *Keyser has no “explicit” “requirement” that “teaches away”*

Despite the clear *in vitro* data, PO has asserted that Iglarz shows that the ET_A/ET_B selectivity for macitentan is “only 50:1.” EX1006, 386. This ratio is based on *in vivo* data, however, and would not have deterred the POSA.

First, PO mischaracterized Keyser, which merely states a preference—not an “explicit requirement”—for ET_A antagonists having selectivity of at least 100. EX1013, ¶¶363-64, 373. Keyser states that “[s]elective compounds for ET_A antagonists ... ***in general, should*** display a relative receptor binding ratio of at least 100, ... ***if*** they are going to act at only one of the receptor subtypes, *e.g.* ET_A.” EX1005, [059] (emphases added). This “general” guidance does not impose a “requirement for ET_A-selective receptor antagonists” or “teach[] away” from the use of all dual receptor antagonists. *Cf.* EX1006, 386; EX1013, ¶¶358-63.

A reference teaches away when the POSA “would be discouraged from following the path set out in the reference,” and if the reference suggests that “the line of development flowing from the reference’s disclosure is unlikely to be productive of the result sought.” *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994) (collecting cases). The mere presence of better alternatives “does not amount to a

teaching away from the lesser preferred but still workable option.” *Bayer Pharma AG v. Watson Labs*, 874 F.3d 1316, 1327 (Fed. Cir. 2017). The law is clear: “A reference that ‘merely expresses a general preference for an alternative invention but does not criticize, discredit, or otherwise discourage investigation into’ the claimed invention does not teach away.” *Meiresonne v. Google, Inc.*, 849 F.3d 1379, 1382 (Fed. Cir. 2017) (citation omitted).

The situation here is akin to that in *Geisler*, where a teaching that “[i]n **general**, the thickness of the protective layer **should** not be less than about [100 Angstroms]” did not teach away from a claimed thickness of 50-100 Angstroms. 116 F.3d at 1471 (emphasis added). Here, neither the “general” guidance nor the statement that a “nonselective antagonist would not function as effectively” (EX1005, [059], [068]) would have led the POSA to simply ignore all antagonists with ratios less than 100. Rather, the POSA had reason to explore ET antagonists having ET_A selectivity ratios of 100 or less because the POSA knew that combinations of a PDE5 inhibitor with bosentan—described by Keyser as having an ET_A selectivity ratio of 20—had been shown to be effective in PAH patients. EX1005, [060]; EX1013, ¶¶362-64; EX1009, EX1010.

In fact, contrary to PO’s argument, all Keyser says is that compounds that are not selective, like bosentan, might not be “**as** effective[.]” EX1005, [068] (emphasis added); EX1013, ¶¶362-63. Keyser prefers compounds with selectivity ratios of 100

or more and states that using bosentan or other compounds with ratios of 20 or less may be less effective, but is silent on compounds with ratios from 20 to 100. Thus, even if the POSA somehow knew of the ratio of 50 only taught in a reference 2 years after the priority date, Keyser does not teach away and Iglarz does not support surprising results.

(3) *PO cannot pick and choose post-priority teachings*

Moreover, even if the POSA were to ignore the *in vitro* nature of the selectivity guidance in Keyser, and rely instead on *in vivo* data in Iglarz cited by PO (EX1006, 386), the POSA would still not be surprised by the results of the macitentan-PDE5 combination disclosed and made obvious by the prior art. Iglarz enables calculating the 1:782 *in vitro* selectivity ratio, but also states that in *in vivo* pharmacology studies, macitentan behaves as a “dual” receptor antagonist. EX1011, 6. According to Iglarz, a 1999 paper by Cardillo, *et al.* taught that “[i]n humans with hypertension, **dual antagonism was superior** to ET_A-selective antagonism in terms of maximal efficacy.” *Id.*, 9.¹⁰ Iglarz explains, citing several pre-priority references,

¹⁰ In rat studies, bosentan required a 10x higher dose than macitentan for the maximum reduction in mean arterial pressure, and the duration of blood pressure response for macitentan was twice as long as for bosentan. *Id.*, 7. Macitentan was “10-fold more potent” and had “2-fold longer duration of action than bosentan.” *Id.*

that dual antagonists are more effective in humans with disease. *Id.*

Thus, if Iglarz may be considered even though it is not prior art, the POSA would know not just that macitentan is a “dual” antagonist, but also that dual antagonists, while possibly inferior-appearing *in vitro*, are more effective in humans with diseases such as hypertension. Knowing that, nothing in Iglarz or Bolli 2012 would teach away from using macitentan in the combinations disclosed in Bolli or Keyser (or Hoeper or Morice, discussed below) for the reasons they provide, including complementary/synergistic effects, fewer side effects, and superior efficacy. If anything, Iglarz would *increase* the POSA’s expectation of efficacy because it teaches that dual antagonists are more effective *in vivo*.

For all these reasons, no secondary considerations, including alleged unexpected results, support nonobviousness. Even if there were unexpected results, they would be insufficient to overcome the strong showing of obviousness.

C. Ground 3: Claims 1-57 Are Obvious Over Hoeper, Morice, and Bolli

The Office has never substantively considered Hoeper or Morice. *Supra* §IV.B.4. As explained below, all challenged claims are obvious over Hoeper, Morice, and Bolli.

1. Claims 1, 6 & 10

a) Claim 1

(1) “A product containing” [1.Preamble]

Hoeper teaches a “product” such as a pharmaceutical composition. EX1009, 1 (describing combining commercially available products bosentan and sildenafil).

Additionally, Morice reports a combination treatment of bosentan and tadalafil. EX1010, 1.

Additionally, Bolli teaches or renders obvious a “product” for the reasons discussed in §V.A.1.a.1. EX1013, ¶¶279-81.

(2) “the compound of formula (I) below ... in free or pharmaceutically acceptable salt form in combination with at least one compound having PDE5-inhibitory properties, in free or a pharmaceutically acceptable salt form” [1.1 & 1.2]

Hoeper teaches the use of an ET antagonist, bosentan, in combination with sildenafil. EX1009, 1 (describing combining bosentan and sildenafil); EX1013, ¶283. Morice teaches bosentan with tadalafil. EX1010, 1. The POSA would know that both sildenafil and tadalafil are PDE5 inhibitors. EX1013, ¶36. Bolli teaches the ET antagonist compound of formula (I) of the ’847 patent—*i.e.*, macitentan—for the reasons discussed in §V.A.1.a.1-2. *Id.*, ¶282.

The POSA had reason to combine Hoeper, Morice, and Bolli because, *inter alia*, Bolli described macitentan as an especially preferred compound. Hoeper and Morice each described beneficial results from combinations involving bosentan.

EX1013, ¶¶284-86. The POSA had reason to use macitentan instead of bosentan because Bolli encouraged use of macitentan (including because its homolog showed potency and ET_A selectivity). EX1013, ¶¶284-86; *supra* §V.B.8.d.1. The POSA would have understood an ET antagonist more potent for ET_A than ET_B to be preferable because it would inhibit vasoconstriction more than vasodilation. EX1013, ¶¶285-86.

(3) “for therapeutic use, simultaneously, separately over a period of time, in the treatment of a disease wherein vasoconstriction is involved” [1.3]

Hoeper describes treatment of patients with a combination of bosentan and sildenafil, and involves administering sildenafil to patients already taking bosentan. EX1009, 1-2. As discussed above, Morice teaches a combination treatment involving simultaneous administration of bosentan and tadalafil. EX1010, 1. Hence, Hoeper and Morice teach simultaneous therapeutic use of a PDE5 inhibitor with an ET antagonist. EX1013, ¶¶289-91.

Element [1.3] is also obvious for the reasons discussed in §§V.A.1.a.4 and V.B.1.a.4, which describe how Bolli alone discloses this limitation in view of the background knowledge and understanding of the POSA. EX1013, ¶¶110-17, 287.

Accordingly, based on the teachings of Hoeper/Morice and Bolli the POSA had reason to simultaneously administer macitentan and a PDE5 inhibitor, such as sildenafil or tadalafil, for treatment and would have expected success in treating

vasoconstrictive diseases. *Id.*, ¶¶289-91.

Hoeper, Morice, and Bolli also render obvious dosing simultaneously, separately, or over a period of time. *Id.*, ¶¶288-95. All of those variable dosage timings are known and obvious in the art, for the reasons discussed above for Grounds 1-2. *Supra* §V.A.1.a.4; EX1001, 2:14-34. Thus, the POSA would have understood that the combinations taught by Hoeper, Morice, and Bolli include simultaneous or approximately at-the-same-time administration of the two drugs. EX1013, ¶¶287-95.

b) Claim 6

The limitations of claim 6 track those of claim 1, and Bolli teaches the limitations of claim 6 for the same reasons as identified above for claim 1. *Id.*, ¶¶302-04. Claim 6 recites a “pharmaceutical composition” containing macitentan and a PDE5 inhibitor as “active principles” along with “at least one excipient.” As described above with respect to claim 1, Hoeper, Morice, and Bolli teach a pharmaceutical composition comprising macitentan and a PDE5 inhibitor. *Supra* §V.C.1.a; EX1013, ¶¶302-06. Bolli further discloses that its pharmaceutical compositions include “at least one excipient.” EX1004, 12; EX1013, ¶304; EX1004, 17-18, claims 12-13, 20.

Additionally, Hoeper and Morice used commercially available dosage forms of Viagra® and Cialis®, which the POSA would have known to contain excipients.

EX1013, ¶305; EX1009; EX1010; EX1007, 1; EX1008, 2.

Accordingly, claim 6 is rendered obvious by Hoeper, Morice, and Bolli.

c) Claim 10

(1) “A method for the treatment of hypertension or pulmonary hypertension comprising” [10.Preamble]

Hoeper, Morice, and Bolli teach methods of treating hypertension or PH involving administration of combinations of an ET antagonist and a PDE5 inhibitor, including a combination of macitentan and sildenafil or tadalafil. *Supra* §V.C.1.a; EX1013, ¶¶311-13.

(2) “administering to a patient in need thereof an effective amount of a compound of formula (I) as described in claim 1, in free or pharmaceutically acceptable salt form” [10.1]

Element [10.1] is obvious for the reasons discussed in §V.C.1.a. *Id.*

(3) “in combination with at least one compound having PDE5-inhibitory properties, in free or pharmaceutically acceptable salt form” [10.2]

Element [10.2] is obvious for the reasons discussed in §V.C.1.a. *Id.*

2. Claims 2-4, 7-9, & 11-13

Claims 2, 7, and 11 recite “the compound having PDE5-inhibitory properties is selected from sildenafil, vardenafil, tadalafil and udenafil.”

Claims 3, 8, and 12 specify tadalafil and claims 4, 9, and 13 specify sildenafil.

As explained above, Hoeper, Morice, and Bolli teach combinations comprising macitentan and one or more vasodilators, such as tadalafil or sildenafil.

Supra §V.C.1.a; EX1013, ¶297. Hoeper expressly teaches combining an ET antagonist with sildenafil and Morice, which responds to and modifies Hoeper’s combination, expressly teaches combining an ET antagonist with tadalafil. EX1009, 1-4; EX1010, 1.

Accordingly, claims 2-4, 7-9, and 11-13 are obvious.

3. Claims 5 & 14-17

Claim 5 recites that the therapeutic use is for at least one of a list of certain vasoconstrictive diseases, including PH and ED.

Claims 14 and 16 specify treatment of PH and claims 15 and 17 further specify treatment of PAH.

Hoeper, Morice, and Bolli teach the limitations of claims 5 and 14-17 for the reasons discussed above regarding claim 1. *Supra* §V.C.1.a; EX1013, ¶¶300, 318-19.

4. Claims 18 & 38

Claims 18 and 38 require “simultaneous” administration of macitentan and tadalafil (claim 18) or sildenafil (claim 38) (*i.e.*, by the same administration route and at the same time). EX1001, 2:15-19.

Bolli discloses macitentan is suitable for oral administration. EX1004, 12; EX1013, ¶¶323-24. Hoeper and Morice also teach oral administration of sildenafil and tadalafil, respectively. EX1009; EX1010. The POSA would thus have been

motivated to administer macitentan and sildenafil or tadalafil by the same route (*e.g.*, orally) performed at the same time for, *e.g.*, patient compliance and convenience. EX1013, ¶325.

Thus, Hoeper, Morice, and Bolli render claims 18 and 38 of the '847 patent obvious.

5. Claims 19 & 39

Claims 19 and 39 require “separate” administration of macitentan and tadalafil (claim 19) or sildenafil (claim 39) (*i.e.*, at approximately the same time by at least two different routes). EX1001, 2:20-24.

As explained above, Hoeper teaches oral administration of bosentan with sildenafil and Morice teaches oral administration of bosentan with tadalafil. *Supra* §V.C.4; EX1009; EX1010. Also as explained above, Bolli teaches that macitentan can be administered by routes other than orally. *Supra* §§V.A.1.a.4, V.A.5, V.C.1.a.3; EX1004, 12. Together, Hoeper, Morice, and Bolli teach treatment methods using different administration routes for macitentan and tadalafil or sildenafil. EX1013, ¶331. The POSA would have found it obvious to administer these drugs at the same time or approximately the same time for, *inter alia*, convenience and patient adherence, and the administration route can be varied for any number of reasons, including convenience, potency, stability, and desired dosing. *Id.*

Thus, Hoeper, Morice, and Bolli render claims 19 and 39 of the '847 patent obvious.

6. Claims 20-22 & 40-42

Claims 20 and 40 require administration of macitentan and tadalafil (claim 20) or sildenafil (claim 40) “over a period of time” (*i.e.*, at different times). EX1001, 2:25-35.

Claims 21 and 22 narrow claim 20 to recite “the interval between administration of the compound of formula (I) and the administration of tadalafil does not exceed two days” (claim 21) and that said interval “does not exceed one day” (claim 22). Claims 41-42 require sildenafil instead of tadalafil but are otherwise identical to claims 21-22.

As explained above, Bolli teaches the limitations of claims 20-22 and 40-42. *Supra* §V.A.6; EX1013, ¶334. For example, morning administration of one drug and evening of the other would satisfy the claims, rendering them obvious. EX1013, ¶¶335-46. Also as explained above, PO acknowledges that administration “over a period of time” was fully within the POSA’s knowledge and capabilities and, in fact, “will have to be determined” for each patient. *Supra* §§V.A.1.a.4, V.A.6; EX1001, 4:7-9; EX1013, ¶325.

Additionally, Hoeper teaches two daily ET antagonist (bosentan) doses and three or four daily doses of sildenafil. EX1009, 2. Hoeper’s method involves

administration over a period of time, at an interval of less than one day apart, since at least one of the daily sildenafil doses is administered without an ET antagonist dose. EX1013, ¶342. Hoeper also discloses that bosentan was administered as a “first-line therapy” before starting sildenafil. EX1009, 1-2; EX1013, ¶342.

Morice modifies Hoeper’s treatment method to substitute once-daily tadalafil for Hoeper’s thrice-daily sildenafil. EX1010, 1. The resulting dosing regimen of once-daily tadalafil and twice-daily ET antagonist (bosentan) thus involves administration over a period of time since at least one of the bosentan doses is administered without tadalafil. EX1013, ¶343. Morice also teaches that the patient started with bosentan only, to which sildenafil was “added.” EX1010, 1. Later, sildenafil was stopped, then restarted, and eventually tadalafil was taken instead of sildenafil. *Id.*; EX1013, ¶343. Thus, the three drugs were taken “over a period of time.”

Because Hoeper and Morice’s administration methods involve daily doses of one drug without the other after or before, on the same day, administering both drugs together, Hoeper, Morice, and Bolli necessarily involve an interval between macitentan and sildenafil or tadalafil doses of less than one day (and thus also less than two days). EX1013, ¶¶340-44.

Hoeper, Morice, and Bolli thus render obvious claims 20-22 and 40-42 of the ’847 patent.

7. Claims 23-37 & 43-57

Claims 23-37 and 43-57 depend from varying parent claims but all recite limitations regarding macitentan and either tadalafil (claims 23-37) or sildenafil (claims 43-57) doses. These claims are obvious over Hoeper, Morice, and Bolli.

Macitentan doses. Claims 23, 26, 29, 32, and 35 recite a macitentan dose range of 0.05mg/kg to 2mg/kg. Claims 25, 28, 31, 34, and 37 recite 0.1mg/kg to 1mg/kg. As explained above, Bolli teaches the macitentan dosage ranges recited in these claims. *Supra* §V.A.7; EX1013, ¶348.

The additional macitentan dosage limitations of claims 43, 45-46, 48-49, 51-52, 54-55, and 57 are identical to the additional limitations of claims 23, 25-26, 28-29, 31-32, 34-35 and 37, respectively.¹¹ Hence, these limitations are obvious over Hoeper, Morice, and Bolli for the same reasons. EX1013, ¶¶348-49.

Tadalafil doses. Claims 24, 27, 30, 33, and 36 recite a tadalafil dose range of 0.01mg/kg to 1mg/kg. These claims are obvious over Hoeper, Morice, and Bolli.

Morice teaches administration of 20mg tadalafil. EX1010, 1. The POSA would have understood Morice's 20mg dose encompasses or overlaps the ranges of claims 24, 27, 30, 33, and 36, based on different body weights. EX1013, ¶¶352-53. For example, administering 20mg to a 70kg patient equates to 0.29mg/kg. *Id.*

¹¹ See *supra*, n.7.

Additionally, the POSA knew the commonly prescribed and commercially available tadalafil (Cialis®) was available in oral tablets in 5mg, 10mg, or 20mg dosages. EX1008, 2; EX1013, ¶353. As evidenced by Morice's 20mg doses, it would have been obvious to use a readily available tadalafil dosage form. EX1013, ¶353. Assuming a standard 70kg mass for an average patient, the 5mg and 20mg dosages equate to a dose range of 0.07mg/kg to 0.29mg/kg. *Id.*, ¶¶352-53. Thus, administration of those 5mg, 10mg, and 20mg dosages encompass or overlap the ranges of claims 24, 27, 30, 33, and 36. *Id.*, ¶¶353-54.

Sildenafil doses. Claims 44, 47, 50, 53, and 56 recite that sildenafil is administered in a dose of 0.1mg to 2mg per kilogram of patient body weight.

Hoeper teaches administration of 25mg or 50mg sildenafil. EX1009, 2. The POSA would have understood Hoeper's disclosed doses encompass or overlap the claimed ranges, based on different body weights. For example, administering 50mg to a 70kg patient equates to 0.71mg/kg. EX1013, ¶355.

Additionally, the POSA knew of the commonly prescribed and commercially available sildenafil products Viagra® and Revatio®. EX1007; EX1025; EX1013, ¶356. The POSA knew Viagra® to be available in oral tablets in 25mg, 50mg, or 100mg dosages and Revatio® is available in a 20mg dosage. EX1007, 1; EX1025, 1; EX1013, ¶357. As evidenced by Hoeper's 25mg and 50mg doses, it would have been obvious to use a readily available sildenafil dosage form. Depending on a

patient's weight and the selected sildenafil dosage, the POSA would have understood Hoeper's treatment method reads on claims 44, 47, 50, 53, and 56. EX1013, ¶356.

Accordingly, claims 23-37 and 43-57 are obvious over Hoeper, Morice, and Bolli. *Id.*, ¶¶351-57.

8. No secondary considerations render any of claims 1-57 non-obvious

As explained in detail above, PO has not shown any secondary considerations which can rescue the '847 claims from a finding of obviousness. *Supra* §V.B.8.

To the extent PO submits evidence related to any alleged secondary consideration, Petitioner reserves the right to submit arguments and evidence in response.

VI. DISCRETIONARY CONSIDERATIONS FAVOR INSTITUTION

Pursuant to Acting Director Coke Stewart's March 26, 2025, Interim Processes for PTAB Workload Management Memorandum, the Office will consider discretionary denial only upon the filing of a brief by PO requesting it. Petitioner will respond if PO files one. The Board should decline to exercise its discretion under 35 U.S.C. §325(d).

VII. MANDATORY NOTICES

A. Real Parties-In-Interest

United Therapeutics Corporation is the real party-in-interest.

B. Related Matters

The challenged patent has not been previously asserted. There are no other granted U.S. patents from the same family as the '847 patent, so no other related patents have been involved in litigation.

C. Counsel

Petitioner provides the following designation of counsel:

Lead Counsel	Back-up Counsel
Douglas H. Carsten MCDERMOTT WILL & EMERY LLP 12636 High Bluff Drive, Suite 325 San Diego, CA 92130 Telephone: (619) 467-1802 Email: dcarsten@mwe.com Facsimile: (858) 720-7800 Registration No. 43,534	Art Dykhuis MCDERMOTT WILL & EMERY LLP 12636 High Bluff Drive, Suite 325 San Diego, CA 92130 Telephone: (619) 467-1803 Email: adykhuis@mwe.com Facsimile: (858) 720-7800 Registration No. 68,325 Adam W. Burrowbridge MCDERMOTT WILL & EMERY LLP 500 North Capitol Street, NW Washington, DC 20001-1531 Telephone: (202) 756-8797 Email: aburrowbride@mwe.com Facsimile: (202) 591-1994 <i>pro hac vice motion forthcoming</i>

D. Service Information

Please address all correspondence to lead counsel's address above. Petitioner also consents to electronic service by email at UTC_847IPR@mwe.com.

VIII. GROUNDS FOR STANDING

Petitioner certifies that the '847 patent is available for IPR and that Petitioner is not barred or estopped from requesting IPR.

IX. FEES

Petitioner authorizes the Office to charge Deposit Account No. 50-0417 for the petition fee set in 37 C.F.R. §42.15(a) and for any other required fees.

X. STATEMENT OF RELIEF REQUESTED

Petitioner requests *inter partes* review of claims 1-57 pursuant to Grounds 1-3 above.

Date: June 10, 2025

Respectfully submitted,

/Douglas H. Carsten/

Douglas H. Carsten

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Counsel for Petitioner

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§42.6 and 42.105, I hereby certify that on June 10, 2025, a copy of the attached PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 8,268,847, together with all exhibits, and all other papers filed therewith, including a Power of Attorney on behalf of Petitioners, was served via Priority Mail Express on the attorneys of record for the patent owner at the following address:

Attorney of Record for Patent Owner

Baker & Hostetler LLP (Customer No. 45511)
1735 Market Street, Suite 3300
Philadelphia, PA 19103-7501

Date: June 10, 2025

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Counsel for Petitioner

CERTIFICATE PURSUANT TO 37 C.F.R. § 42.11

Pursuant 37 C.F.R. § 42.11, the undersigned certifies that this PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 8,268,847, and accompanying evidence are not being presented for an improper purpose and that all legal contentions, allegations, and denials are warranted and have evidentiary support.

Date: June 10, 2025

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Counsel for Petitioner

CERTIFICATE PURSUANT TO 37 C.F.R. § 42.24(d)

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that this PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 8,268,847, complies with the type-volume limitation of 37 C.F.R. § 42.24(a). The word count application of the word processing program used to prepare this paper states that the paper contains 13,970/14,000 words, excluding the parts of the paper exempted by 37 C.F.R. §§ 42.24(a)(1).

Date: June 10, 2025

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