

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

**DECLARATION OF DR. RONALD J. SHEBUSKI, SR IN SUPPORT OF
PETITION FOR INTER PARTES REVIEW**

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DECLARATION OF DR. RONALD J. SHEBUSKI, SR

I, Ronald J. Shebuski, SR, Ph.D., hereby declare under penalty of perjury that the following statements are made based on my personal knowledge and are true and correct.

I. Introduction and Qualifications

1. I have been retained by McDermott Will & Emery LLP on behalf of United Therapeutics Corporation (“UTC”) to provide an analysis of U.S. Patent No. 8,268,847 (“the ’847 patent”).

2. I am being compensated at my standard hourly rate of \$450.00 per hour for my time. My compensation is not in any way contingent on my performance, the result of this proceeding, or any of the issues involved therein. I am also being reimbursed for expenses incurred as a result of activities performed as an expert.

3. I understand that UTC is asserting three grounds of unpatentability in this *inter partes* review (“IPR”) challenging claims 1-57 of the ’847 patent. In particular, I understand that UTC asserts that claims 1-57 of the ’847 patent are anticipated by or obvious over certain prior art references.

4. My education and technical experience are described in my Curriculum Vitae (“CV”), which is attached to this Report as Appendix A. As a staff Research Scientist at large pharmaceutical companies (Smith Kline & French Laboratories, Inc. and Merck; 1985-1990), and later as Director, Cardiovascular Pharmacology

(Pharmacia & Upjohn, Inc.; 1990-1998), my primary responsibilities were to manage and oversee drug discovery and development efforts of cardiovascular projects running simultaneously in my group(s). Those efforts involved high throughput drug screening (“HTS”), *in vitro* cell- or tissue-based drug candidate assays (as described above), and *in vivo* drug candidate evaluation of efficacy and preliminary safety. In this capacity, I also worked closely with medicinal chemists who were determining structure activity relationships (“SAR”) for the drug targets we were pursuing. I reviewed results of HTS (accomplished in house or at contract research organizations), identified compounds to move to *in vitro* cell or tissue-based assays, and eventually selected compounds for *in vivo* evaluation of pharmacokinetics, pharmacological efficacy (pharmacodynamics), and preliminary safety in animal models. I have published extensively on various stages of drug discovery. My publications include studies related to small molecule, peptide and antibody approaches for pharmaceutical design, testing, evaluation of pharmacokinetics, pharmacology, preclinical safety and efficacy for various molecules and drug candidates. Additionally, I examined the results of HTS efforts and chose compounds with the greatest potency and selectivity towards the receptor or target being examined for further development *in vitro*, *ex vivo*, and *in vivo*.

5. My expertise in pharmacology also lends itself well to toxicological and clinical studies where I suggest starting doses of the drug candidate based on

previous pre-clinical pharmacology dose-response evaluations accomplished in relevant animal models.

6. I am also experienced in and educate others with regards to the use of animal models to study safety and efficacy of drug candidates. Specifically, I have published frequently on the development and application of animal models for medicinal research. This work includes how non-human primates, pigs, dogs, rabbits, guinea pigs, rats, and mice can be used to study the effect of various proteins, antibodies, and other small molecules *in vivo*.

II. Materials Considered

7. The opinions contained in this Declaration are based on the documents I reviewed, my knowledge and experience, and professional judgment. In forming the opinions expressed in this Declaration, while drawing on my experience, I reviewed the following documents:

Exhibit	Description
EX1001	U.S. Patent No. 8,268,847 to Clozel (“’847 patent”)
EX1002	Prosecution History of the ’847 patent
EX1003	Prosecution History of U.S. Reexamination Application No. 96/000,237
EX1004	WO2002/053557 (“Bolli”)
EX1005	WO2006/026395 (“Keyser”)
EX1006	Prosecution History of U.S. Application No. 13/604,148 (“’148 Application”)

Exhibit	Description
EX1007	Prescribing Information for Viagra® (Nov. 1998) (“Viagra®”)
EX1008	Prescribing Information for Cialis® (Nov. 2003) (“Cialis®”)
EX1009	M.M. Hoeper et al., <i>Combination Therapy with Bosentan and Sildenafil in Idiopathic Pulmonary Arterial Hypertension</i> , 24 EUR. RESPIRATORY J. 1007 (2004) (“Hoeper”)
EX1010	A.H. Morice et al., Letter to the Editors, <i>Combination Therapy with Bosentan and Phosphodiesterase-5 Inhibitor in Pulmonary Arterial Hypertension</i> , 26 EUR. RESPIRATORY J. 180 (2005) (“Morice”)
EX1011	Marc Iglarz et al., <i>Pharmacology of Macitentan, an Orally Active Tissue-Targeting Dual Endothelin Receptor Antagonist</i> , 329 J. PHARMACOLOGY & EXPERIMENTAL THERAPEUTICS 736 (2008) (“Iglarz”)
EX1014	K. Lunze et al., <i>First Experience with an Oral Combination Therapy Using Bosentan and Sildenafil for Pulmonary Arterial Hypertension</i> , 36 EUR. J. CLIN. INVEST. 32 (2006)
EX1015	EP1097711A2
EX1016	Parthipan Kanthapillai & E. Haydn Walters, <i>Phosphodiesterase 5 Inhibitors for Pulmonary Hypertension (Review)</i> , COCHRANE DATABASE SYSTEMATIC REV., Oct. 18, 2004 at 1–22
EX1017	Audrey J. Lee et al., <i>Sildenafil for Pulmonary Hypertension</i> , 9 ANNALS OF PHARMACOTHERAPY 869 (2005)
EX1018	Aaron L. Trachte et al., <i>Oral Sildenafil Reduces Pulmonary Hypertension After Cardiac Surgery</i> , 79 ANNALS OF THORACIC SURGERY 194 (2005)
EX1019	Emiliano Antonia Palmieri et al., Letter to the Editor, <i>Tadalafil in Primary Pulmonary Arterial Hypertension</i> , 141 ANNALS OF INTERNAL MED. 743 (2004)

Exhibit	Description
EX1020	Alain Daugan et al., <i>The Discovery of Tadalafil: A Novel and Highly Selective PDE5 Inhibitor. 1: 5,6,11,11a-Tetrahydro-1H-imidazol[1',5':1,6]pyrido[3,4-b]indole-1,4-dione Analogues</i> , 46 J. MED. CHEM. 4525 (2003)
EX1021	Evangelos Michelakis et al., <i>Oral Sildenafil Is an Effective and Specific Pulmonary Vasodilator in Patients with Pulmonary Arterial Hypertension: Comparison with Inhaled Nitric Oxide</i> , 105 CIRCULATION 2398 (2002)
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")
EX1026	J.D. Corbin, <i>Mechanisms of Action of PDE5 Inhibition in Erectile Dysfunction</i> , 16 INT. J. IMPOTENCE RSCH. S4 (2004)
EX1027	Rafal M. Kedzierski & Masashi Yanagisawa, <i>Endothelin System: The Double-Edged Sword in Health and Disease</i> , 41 ANN. REV. PHARMACOLOGY & TOXICOLOGY 851 (2001)
EX1028	Bonggwan Seo et al., <i>Both ET_A and ET_B Receptors Mediate Contraction to Endothelin-1 in Human Blood Vessels</i> , 89 BASIC SCI. REP. 1203 (1994)
EX1029	Carmine Cardillo et al., <i>Interactions Between Nitric Oxide and Endothelin in the Regulation of Vascular Tone of Human Resistance Vessels In Vivo</i> , 35 HYPERTENSION 1237 (2000)

Exhibit	Description
EX1030	P.J. Henry, <i>Endothelin Receptor Distribution and Function in the Airways</i> , 26 CLIN. & EXPERIMENTAL PHARMACOLOGY & PHYSIOLOGY 162 (1999)
EX1031	Jean-Philippe Gratton et al., <i>ET_B Receptor and Nitric Oxide Synthase Blockade Induce BQ-123–Sensitive Pressor Effects in the Rabbit</i> , 30 HYPERTENSION 1204 (1997)
EX1032	Nazzareno Galié et al., <i>Ambrisentan Therapy for Pulmonary Hypertension</i> , 46 J. AM. COLL. CARDIOLOGY 529 (2005)
EX1033	Christopher F. Barnett & Roberto F. Machado, <i>Sildenafil in the Treatment of Pulmonary Hypertension</i> , 2 VASCULAR HEALTH & RISK MGMT. 411 (2006)
EX1034	M.C. Berenbaum, <i>What is Synergy?</i> , 41 PHARMACOLOGICAL REV. 93 (1989)
EX1035	William R. Greco et al., <i>The Search for Synergy: A Critical Review from a Response Surface Perspective</i> , 47 PHARMACOLOGICAL REV. 331 (1995)
EX1036	Jackie D. Corbin et al., <i>High Lung PDE5: A Strong Basis for Treating Pulmonary Hypertension with PDE5 Inhibitors</i> , 334 BIOCHEMICAL & BIOPHYSICAL RSCH. COMMUN. 930 (2005)
EX1037	S. Thomas Forgue et al., <i>Tadalafil Pharmacokinetics in Healthy Subjects</i> , 61 BRIT. J. CLIN. PHARMACOLOGY 243 (2006)
EX1038	Judy W.M. Cheng, <i>Bosentan</i> , 3 HEART DISEASE 161 (2003)
EX1039	Wolfgang Kiowski et al., <i>Endothelin-1-Induced Vasoconstriction in Humans</i> , 83 CIRCULATION 471 (1991)
EX1040	Morris C. Berenbaum, <i>The Expected Effect of a Combination of Agents: The General Solution</i> , 114 J. THEORETICAL BIOLOGY 413 (1985)
EX1041	Nazzareno Galié et al., <i>Sildenafil Citrate Therapy for Pulmonary Arterial Hypertension</i> , 353 N. ENGL. J. MED. 2148 (2005)

Exhibit	Description
EX1042	F. Affuso et al., <i>Tadalafil Improves Quality of Life and Exercise Tolerance in Idiopathic Pulmonary Arterial Hypertension</i> , 108 INT J. CARDIOL. 429 (2006)
EX1043	U.S. Patent No. 5,250,534 to Bell
EX1044	Nazzareno Galiè et al., <i>Comparative Analysis of Clinical Trials and Evidence-Based Treatment Algorithm in Pulmonary Arterial Hypertension</i> , 43 J. AM. COLL. CARDIOLOGY 81S (2004)
EX1045	Approval Letter, Application Number 21-290, U.S. FOOD & DRUG ADMIN. (2001)
EX1046	Therese Ringbom et al., <i>Ursolic Acid from Plantago major, a Selective Inhibitor of Cyclooxygenase-2 Catalyzed Prostaglandin Biosynthesis</i> , 61 J. NAT. PROD. 1212 (1998)
EX1047	M.M. Hoeper et al., <i>Combination Therapy with Bosentan and Sildenafil in Idiopathic Pulmonary Arterial Hypertension</i> , 24 EUR. RESPIRATORY J. 1007 (2004) (date-stamped copy)
EX1048	A.H. Morice et al., Letter to the Editors, <i>Combination Therapy with Bosentan and Phosphodiesterase-5 Inhibitor in Pulmonary Arterial Hypertension</i> , 26 EUR. RESPIRATORY J. 180 (2005) (date-stamped copy)

III. Understanding of Governing Law

8. I offer no opinion on the law itself because I am not an attorney and do not have formal legal training. Counsel has provided the following understanding of law to me, and I subsequently applied this understanding in my analysis.

A. Person of Ordinary Skill in the Art

9. I understand from counsel that my analysis must be performed from the perspective of a hypothetical “person of ordinary skill in the art” (“POSA”) as of the

priority date. In other words, I understand that my analysis should not be performed using a present-day perspective, and that I should not use hindsight or the perspective of the most knowledgeable experts in the field. Rather, my analysis should be done as of the priority date using only information known as of that time and applying ordinary skill and expertise.

10. I understand that the level of ordinary skill depends on several factors, including: (1) the level of education of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field.

11. I understand that the POSA is a hypothetical person who is presumed to be aware of all pertinent prior art, has ordinary skill in the field of the invention, and is a person of ordinary creativity.

B. Priority

12. I understand from counsel that there are various types of patent applications and that, after consideration by the U.S. Patent and Trademark Office, a patent will eventually be allowed and issue.

13. For purposes of determining what the POSA would know, I understand that any documents or references must pre-date the patent. For that purpose, I understand from counsel that the relevant date is not when the patent issued, but the

date of the earliest application that described the claimed invention. I understand this relevant date is referred to as the priority date.

14. To determine which application(s) establish the priority date for a patent, counsel has informed me that a patent is entitled to the filing date of its earliest-filed application so long as the earlier-filed application describes the claimed invention to the POSA, who reads the application from the perspective of ordinary knowledge and creativity.

15. I have been asked to assume that the priority date for all claims of the '847 patent is August 29, 2006.

C. Anticipation

16. I understand from counsel that a patent claim is unpatentable as “anticipated” under 35 U.S.C. § 102 if each and every element of a claim, as properly construed, is found either explicitly or inherently in a single prior art reference. A reference explicitly discloses a claim element if the element is described in the reference. A reference inherently discloses a claim element, even if that element is not explicitly present, if the disclosures in the reference necessarily function in accordance with, or includes, the claimed elements. I also understand from counsel that an anticipation analysis is done from the perspective of the POSA—*i.e.*, whether the POSA would understand the prior art reference to disclose the limitation in question. Along those lines, I also understand from counsel that a prior art reference

with a generic disclosure of some element anticipates a more-specific claim limitation if the more-specific limitation would be immediately apparent to the POSA from the disclosure.

D. Obviousness

17. I understand from counsel that a patent claim is unpatentable as “obvious” under 35 U.S.C. § 103 in light of one or more prior art references if it would have been obvious to the POSA at the time of the alleged invention, taking into account (1) the scope and content of the prior art, (2) the differences between the prior art and the claims, (3) the level of ordinary skill in the art, and (4) any so called “secondary considerations” of non-obviousness, which include “long felt need” for the claimed invention, commercial success attributable to the claimed invention, unexpected results of the claimed invention, skepticism of others, failure by others to achieve the claimed invention, and “copying” of the claimed invention by others.

18. I understand from counsel that a claim can be obvious in light of a single prior art reference or multiple prior art references. To be obvious in light of a single prior art reference or multiple prior art references, there must be a reason that would have prompted the POSA to modify the single prior art reference, or combine two or more references, in a manner that provides the elements of the claimed invention. This reason may come from a teaching, suggestion, or motivation to combine, the

reference(s) themselves, the knowledge or “common sense” of the POSA, or from the nature of the problem to be solved. The reason that would have prompted the POSA to modify the single prior art reference or combine two or more references may be explicit or implicit from the prior art as a whole. I have been informed that, under the law, the combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results. I also understand it is improper to rely on hindsight in making the obviousness determination.

E. Claim Construction

19. I understand from counsel that the claims of the '847 patent must be interpreted from the perspective of the POSA as of the priority date. I also understand from counsel that the Board presiding over this IPR may engage in claim construction. I understand that the relevant inquiry in claim construction is the question of how the POSA would have understood the claim terms at the time of the earliest priority date, in light of the patent specification, the prosecution history, and any other relevant intrinsic and extrinsic evidence.

20. I further understand that patent applicants can define terms in the specification of the patent. Here, the '847 patent provides definitions for several terms, including “PDE-5,” “simultaneously” or “simultaneous,” “separately” or “separate,” “over a period of time,” “disease where vasoconstriction is involved,”

“compound having PDE5-inhibitory properties,” and “pharmaceutically acceptable salts.” EX1001, 2:6-3:31. I have reviewed those definitions and adopted them for purposes of my analysis. Generally, the POSA would find these definitions to comport with the plain and ordinary meaning of the terms, other than “over a period of time,” which has a broad definition that includes months of time between administrations. Other than adopting those terms’ definitions from the patent itself, I have been asked to give the remaining claim terms their plain and ordinary meaning as would be understood by a person of ordinary skill in the art.

IV. The Person of Ordinary Skill in the Art

21. The ’847 patent relates to treatment of diseases involving vasoconstriction, which includes pulmonary hypertension (“PH”), pulmonary arterial hypertension (“PAH”), diabetic arteriopathy, heart failure, erectile dysfunction (“ED”), and angina pectoris (*i.e.*, chest pain).

22. The POSA would be expected to 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. Cardiovascular and/or pulmonary conditions, include, *e.g.*, hypertension, PH, 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.

23. I exceed the POSA's level of skill and experience as is clear from my CV (Appendix A) and for the reasons described above in Section I. For example, I have more than 20 years of experience in drug development for cardiovascular conditions through my work with large pharmaceutical companies and consulting.

V. Technology Overview

24. The following is a description of background information known to the POSA as of the priority date. *See supra* §III.B, above.

25. The '847 patent refers to at least two types of drugs: (1) endothelin receptor antagonists and (2) phosphodiesterase type 5 ("PDE5") inhibitors.

A. Endothelin Receptor Antagonists

26. Well before the '847 patent's priority date, the POSA would have known that endothelin is a potent vasoconstrictor that may bind to two receptor subtypes, ET_A and ET_B, and is also implicated in diseases involving vasoconstriction. EX1028, 1. Endothelin is a small peptide that has "an array of physiological functions, with roles in basal vascular tone, sodium balance, neural crest cell development, and neurotransmission." EX1027, 1. Endothelin is produced primarily by vascular endothelial cells and has been characterized as a powerful vasoconstrictor and mitogen (*i.e.*, a substance which induces cell division or

enhances the rate of cell division) for smooth muscle. EX1032, 1. “Activation of the [endothelin] system has been shown in both plasma [] and lung tissue [] of PAH patients, as well as in animal models of PAH, [thereby] supporting a prominent role of endothelin in the pathogenesis of this condition.” *Id.* There are various forms of endothelin, including ET-1, ET-2, and ET-3. *See* EX1027, 2; EX1005, [010]. Endothelin receptors modulate divergent vascular roles with ET_A activation in smooth muscle cells by primarily ET-1. EX1038, 1-2; EX1032, 1. Activation of ET_B receptors on blood vessel endothelium by ET-1 results in vasodilation per release of endogenous endothelial-derived agents such as prostacyclin and nitric oxide. EX1028, 1; EX1032, 1.

27. Prior to the '847 patent's priority date, the POSA knew that ET-1 played a critical role in vasoconstrictive diseases (*e.g.*, PH, ED), which are typically characterized by an overproduction of ET-1. EX1027, 6. ET_A receptors, which are primarily located on vascular smooth muscle cells, mediate these vasoconstrictive effects when activated by ET-1. *Id.* at 6-7. Persistent activation of ET_A receptors by ET-1 in airway smooth muscle can lead to PAH. *Id.* at 11. Endothelial dysfunction can lead to loss of ET_B receptor mediated release of endogenous vasodilators described above. EX1031, 2.

28. The POSA would have also known that blocking the ET_A receptor with an endothelin receptor antagonist helps prevent this vasoconstriction, thereby

improving blood flow and reducing pulmonary pressure. For example, the POSA would have known of previous methods for effectively treating diseases involving vasoconstriction like PAH by administering, *e.g.*, endothelin receptor antagonists such as bosentan. *See, e.g.*, EX1038; EX1044.

29. ET_A and ET_B receptors are G protein-coupled receptors (“GPCRs”), which are composed of seven transmembrane domain receptors that detect molecules outside the cell and activate intracellular responses coupled with G proteins. EX1028, 1; EX1027, 3.

30. ET_A and ET_B receptors are located on smooth muscle cells and mediate vascular contraction (*i.e.*, vasoconstriction) in response to binding to ET-1. ET_B receptors appear on blood vessel endothelium and are involved in mediating release of vasodilatory nitric oxide to relax smooth muscle in blood vessels resulting in decreased vascular resistance to improve blood flow and reduce pulmonary or arterial blood pressure.

31. In the vascular system, both receptors are coupled to downstream G proteins which have opposing functions. ET_A primarily mediates vasoconstriction per elevation of intracellular calcium by irreversible binding to ET-1. *See* EX1038, 1; EX1039, 5-6. Conversely, endothelial ET_B induces vasorelaxation, also referred to as vasodilation, primarily through elaboration of the nitric oxide and prostacyclin mediated pathways, which results in elevation of cyclic guanosine monophosphate

("cGMP") and cyclic adenosine monophosphate respectively. *E.g.*, EX1028, 1; EX1029, 1.

32. Vasodilation is associated with increased blood flow as the resistance to flow has been lowered by the smooth muscle cell relaxation. Importantly, smooth muscle cells are located in blood vessels and pulmonary airways such that dual benefit occurs by eliciting smooth muscle cell relaxation in blood vessels and airways. Within the lung, ET-1 is synthesized and released by airway epithelial and vascular endothelial cells which are both located in proximity to airway and vascular smooth muscle cells. EX1030, 1.

33. A POSA would have understood that inhibition of ET_A receptors would relieve vasoconstriction and would, therefore, lower blood pressure. Inhibition of ET_B receptors would be considered counter-productive for lowering blood pressure as the vasodilatory effects of nitric oxide or prostacyclin would be negated. *See, e.g.*, EX1031, 2.

34. In view of this background, the POSA looking to improve blood flow would have understood that an endothelin receptor antagonist that is more potent for ET_A than ET_B, would be preferable because an ET_A antagonist would preferentially inhibit vasoconstriction. The antagonism of the ET_B receptor could negate the beneficial actions of endogenous vasodilators such as nitric oxide and prostacyclin, so the POSA would explore endothelin receptor antagonists having greater potency

for ET_A than for ET_B. As I explain further below, the POSA would have looked to different antagonists' IC₅₀ (half maximal Inhibitory Concentration) values for ET_A and ET_B when considering compounds suitable to treat conditions involving vasoconstriction (*e.g.*, by blocking the vasoconstrictive effects of ET-1).

B. PDE5 Inhibitors

35. The POSA also would have understood that the enzyme PDE5 breaks down cGMP, and that PDE5 inhibitors inhibit PDE5. By inhibiting PDE5, cGMP levels rise, leading to smooth muscle relaxation and vasodilation, and improving blood flow. EX1026, 1.

36. PDE5 inhibitors are well understood and widely prescribed vasodilators for the treatment of ED, and that was also the case as of the priority date. As of the priority date, common PDE5 inhibitors include sildenafil (Viagra®) and tadalafil (Cialis®). EX1007, 1; EX1008, 2; EX1020, 1; EX1023, 1-4; EX1041, 1.

37. Additionally, combining two or more compounds having different mechanisms of action for treatment of the same type of disease is a matter of mere common sense to the POSA. *See e.g.*, EX1034, 1; EX1044, 5. The POSA would be motivated to combine drugs having distinct mechanisms of action because the POSA is seeking to maximize therapeutic effect and understands that combining drugs with different mechanisms of action or which act on different biological pathways is a logical way to achieve that goal. *See e.g.*, EX1014, 1.

38. Prior to the '847 patent's priority date, the POSA would have understood a combination therapy comprising an endothelin antagonist and a PDE5 inhibitor to target two distinct pathways involved in vascular tone regulation—*i.e.*, inhibiting the vasoconstrictive effect of ET-1 and enhancing the vasodilatory effects of nitric oxide mediated by cGMP. EX1014, 2; EX1016, 5. The POSA would have expected such a combination of drugs to be complementary. This combination of drugs would be complementary because while the endothelin receptor antagonist directly blocks the vasoconstrictive effect of ET-1, the PDE5 inhibitor concomitantly enhances the vasodilatory effects of cGMP by preventing degradation of nitric oxide. EX1014, 2, 5; EX1018, 1; EX1030, 5. The POSA would at minimum have known that those two classes could be synergistic and would have reasonably expected such a combination of drugs to work together synergistically—*i.e.*, to reduce blood pressure to an extent greater than the sum of the effects of an endothelin receptor antagonist alone and a PDE5 inhibitor alone. EX1034, 3.

C. IC₅₀ Values and Selectivity Ratios

39. During drug development, scientists assess which of many candidate compounds are more promising and likely to work as an effective drug. One such measure, IC₅₀, is a way of analyzing the potency of a drug.

40. IC₅₀ stands for “half-maximal inhibitory concentration” and in the context of therapeutic agents, IC₅₀ is a value used to describe the potency of a

compound in inhibiting a specific biological or biochemical function. *See e.g.*, EX1020, 3-4. A drug's IC_{50} value indicates the amount or concentration of a drug needed to achieve a 50% inhibition of the target function (*e.g.*, blocking of 50% of endothelin receptors in a sample). Accordingly, the lower the IC_{50} value for a given compound, the more potent the compound is at achieving the desired inhibitory effect (*i.e.*, less drug needed for the same effect). *Id.* The POSA would have used IC_{50} values to compare the potencies of different compounds for a common target or result.

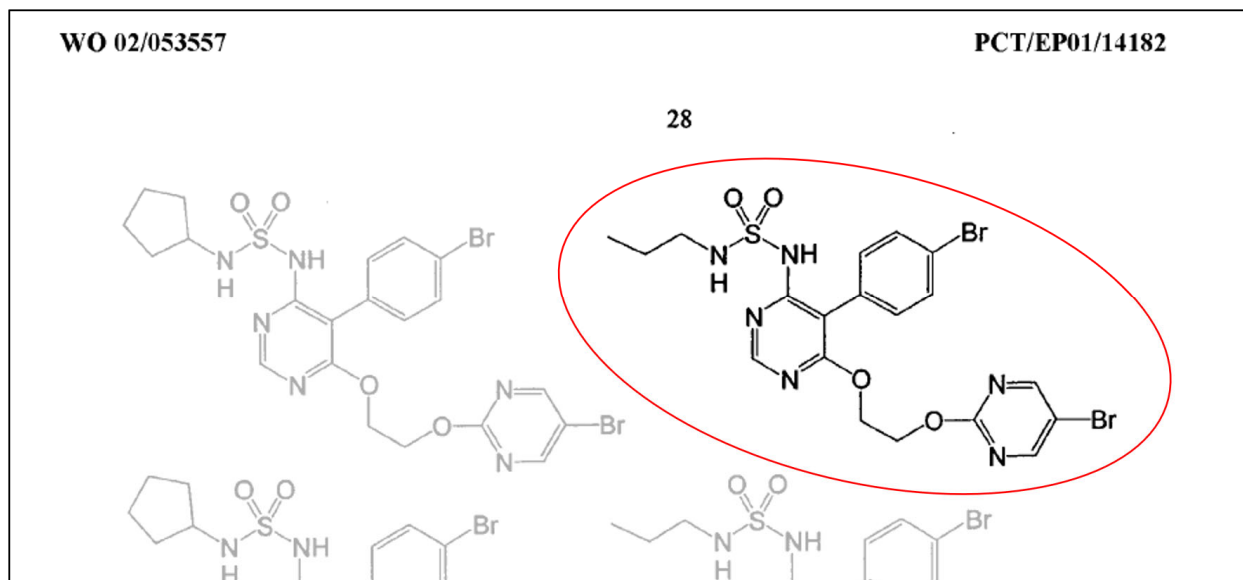
41. When a drug has an inhibitory effect on more than one target, an IC_{50} value can be obtained for each target and the relative potency can be assessed. The relative potency of a compound for one target versus another can be understood as the compound's selectivity for one target over the other. Dividing a larger IC_{50} value for a first target by a smaller IC_{50} value for a second target provides the relative selectivity (or "selectivity ratio") for the second target as compared to the first. *See e.g.*, EX1046, 1-2.

42. Hence, the quotient of ET_B IC_{50} divided by ET_A IC_{50} value represents the selectivity of an endothelin receptor antagonist for ET_A , with a higher quotient (*i.e.*, the selectivity ratio) indicating greater ET_A selectivity. *See e.g.*, EX1020, 3-4; EX1028, 2; EX1046, 1-2.

D. Prior Art

1. Bolli (EX1004)

43. Bolli is an international PCT patent application publication, entitled “Novel Sulfamides And Their Use As Endothelin Receptor Antagonists.” EX1004, [54]. I understand that Bolli published on July 11, 2002, and further understand from counsel that Bolli’s publication date makes it prior art under 35 U.S.C. §§102(a), (b), and (e). *Id.*, [43]. Bolli describes “novel pyrimidine-sulfamides of the general formula I and their use as active ingredients in the preparation of pharmaceutical compositions.” EX1004, 2. Bolli further discloses “pharmaceutical compositions containing one or more compounds of the general formula I and especially their use as endothelin receptor antagonists.” *Id.* As example compounds of “general formula (I),” Bolli teaches an “especially preferred group of compounds” further defined by “formula V,” which defines a subset of the formula (I) compounds. *Id.*, 22. Macitentan is a member of formula V and is disclosed by Bolli as a “preferred compound”:



Id., 29 (annotation added); *see also* EX1002, 141 (“Bolli et al. teach the Applicant’s compound as an ET antagonist (see page 28, first row, right compound).”). Bolli also teaches that drugs such as macitentan may be combined with vasodilators to treat diseases involving vasoconstriction. EX1004, 18.

44. Bolli teaches procedures for demonstrating “inhibitory activity of the compounds of general formula I on endothelin receptors” including “the evaluation of the potency and efficacy of the compounds of the general formula I.” EX1004, 3-4; *see also id.*, 1-11, Table 1. In Table 1, Bolli discloses IC₅₀ values for ET_A and ET_B obtained with certain compounds of general formulae I and V (*id.*, 5-9), including Example 104 (*id.*, 7). Table 1 shows that Example 104 is highly selective for ET_A, with an IC₅₀ value of only 0.88, compared to 601 for ET_B (a ratio of 601/0.88 = 683). EX1004, 7. As I explain in detail below, Example 104 is the compound in Table 1

that is the most similar to macitentan. *See infra* §VII.C.1.a.2, §VII.D; *see id.*, 7 (disclosing IC₅₀ values for Example 104) and 94 (disclosing the structure of Example 104).

2. Keyser (EX1005)

45. Keyser is a PCT patent application publication titled “Endothelin A Receptor (ET_A) Antagonists In Combination With Phosphodiesterase 5 Inhibitors (PDE5) And Uses Thereof.” EX1005, [54]. I understand that Keyser published on March 9, 2006, and is therefore prior art under pre-AIA 35 U.S.C. §§102(a) and (e). *Id.*, [43].

46. Keyser teaches “combination therapies comprising an endothelin A receptor (ET_A) antagonist and a phosphodiesterase 5 (PDE5) inhibitor, pharmaceutical compositions comprising [an] ET_A antagonist and [a] PDE5 inhibitor and methods of treating various disorders comprising administering an ET_A antagonist and a PDE5 inhibitor. In particular, the combination therapies and pharmaceutical compositions are useful for the treatment and/or prevention of cardiac disorders such as pulmonary arterial hypertension (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. *See id.*, [009]. To solve this problem, Keyser teaches a complementary treatment combining a PDE5 inhibitor with an ET_A antagonist to

reduce dosages and side effects. *Id.*; *see also id.*, [067]. Keyser includes data from a pharmacokinetic drug interaction study showing the combination of sitaxsentan (an ET_A antagonist) with sildenafil (a PDE5 inhibitor) was well-tolerated. *See, e.g., id.*, [093]-[097] (Example 1).

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

47. Food and Drug Administration (FDA) approved the citrate salt of sildenafil to treat ED under the brand name Viagra® in 1998, (EX1007, 19) and tadalafil to treat ED under the brand name Cialis® in 2003, (EX1008, 26). By 2000, a mere two years after launch, Viagra® was ubiquitously known, as evidenced by skyrocketing consumer prescriptions and impressive sales numbers. EX1023, 1-2. Tadalafil was also studied and used to treat PH. EX1010, 1; EX1019, 6. Sildenafil and tadalafil are PDE5 inhibitors. *See* EX1007, 1; EX1008, 2. The commercial success of both Viagra® and Cialis®, and the public's general knowledge of them as of the presumed priority date, would have motivated the POSA to further investigate these particular products in greater levels of detail than other drugs in order to knowledgeably speak to them and refer them to patients.

48. 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). And

sildenafil was known to have “vasodilatory properties” that could have an effect on patients with “underlying cardiovascular disease.” EX1007, 11.

49. FDA also approved the citrate salt of sildenafil to treat PAH under the brand name Revatio® in 2005. EX1025, 1, 13.

4. Hoeper (EX1009) and Morice (EX1010)

50. 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).¹ Both were published in the European Respiratory Journal, indexed in a library, and available online. EX1009; EX1047; EX1010; EX1048. I understand that both Hoeper and Morice are prior art under pre-AIA §102(a) and §102(b).

51. Hoeper teaches the combination of substances having “different mechanisms of action,” including a combination therapy involving administration of both bosentan (an endothelin receptor antagonist) and sildenafil (a PDE5 inhibitor). EX1009, 1-3. Hoeper provides several rationales for choosing bosentan and sildenafil, including the fact that “both substances are orally available, act via

¹ Petitioner submits two copies of Morice and Hoeper. Citations to EX1009 and EX1010 apply equally to EX1047 and EX1048 respectively.

different mechanisms and are usually well tolerated,” and concludes that the disclosed bosentan/sildenafil combination is safe and effective in patients with idiopathic pulmonary arterial hypertension (“IPAH”). *See id.*, 1, 4.

52. As Hoeper explains, when a population of 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. According to the data presented by Hoeper *et al.*, the bosentan/sildenafil 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.

53. Submitted as a comment on Hoeper, Morice further discloses a combination treatment of bosentan and tadalafil. *See* EX1010, 1. Morice found that the combination treatment of bosentan and tadalafil resulted in an “excellent symptomatic response” and a maintained reduction in pulmonary artery pressure in the patient. *Id.* (noting a reduced pulmonary artery pressure of 61 mmHg, down from 100).

VI. The ’847 Patent

A. Prosecution History

54. The issue date on the first page of the ’847 patent is September 18, 2012. The patent issued from U.S. Application No. 12/439,290 (“’290 Application”),

which was a PCT application filed on August 28, 2007. EX1001, 1. The '847 patent claims priority to PCT/IB2006/052999, which was filed on August 29, 2006. *Id.*

1. '847 Patent Prosecution

a) Non-Final Office Action

55. The first substantive action in the prosecution of the '847 patent was a Non-Final Office Action which had an obviousness rejection over Bolli in view of Keyser. EX1002, 140-41. The examiner asserted that Bolli teaches the compound of formula (I)—*i.e.*, macitentan—of the '847 patent as an endothelin receptor antagonist used to treat conditions associated with vasoconstriction. *Id.*, 141. Likewise, Keyser teaches an endothelin receptor antagonist and PDE5 inhibitors can be combined to treat cardiac disorders. *Id.* The examiner concluded that it would be obvious to one skilled in the art to combine the disclosed compound (macitentan), which is an ET antagonist, and a PDE5 inhibitor in light of Bolli and Keyser. *Id.*

b) Patent Owner's Response to the Non-Final Office Action

56. In response, the Patent Owner asserted that Bolli did not qualify as prior art under 35 U.S.C. 103(c) because it was “either owned by Actelion or subject to an obligation to assign the invention to Actelion at the time the invention was made.” *Id.*, 207.

c) Patent Office Final Office Action

57. After Patent Owner's response, the examiner issued a Final Office

Action. That Final Office Action continued to assert that the claims in the application were obvious. *Id.*, 227. Specifically, the examiner pointed out that the compound disclosed in Bolli had a relative receptor binding ratio that was preferable according to Keyser. *Id.*, 228. This indicated, according to the examiner, that there was a strong motivation to combine the Patent Owner's compound with a PDE5 inhibitor. *Id.*

d) Response to Final Office Action

58. In response, the Patent Owner asserted that the claimed compound and that the compound disclosed in Bolli were not the same. *Id.*, 238. The Patent Owner pointed out that the Bolli compound has a methyl-sulfamic acid amide while the claimed compound has an n-propyl -sulfamic acid amide group. *Id.* Furthermore, the Patent Owner argued that while the disclosed compound met the ET_A/ET_B selectivity ratio of Keyser, there were several other compounds mentioned in Bolli that also met this standard. *Id.* Therefore, the Patent Owner maintained that there was no motivation to combine the claimed compound over any of the other disclosed Bolli compounds. *Id.*, 239.

e) Allowance

59. The Patent Office issued a Notice of Allowance on May 21, 2012. *Id.*, 298. In allowing the '290 Application, the examiner relied on the Patent Owner's assertion that Bolli did not qualify as prior art under 35 U.S.C. §103(c). *Id.*, 303. There was no discussion of whether Bolli qualified as prior art under 35 U.S.C.

§§102(a) or 102(b). *Id.*

2. Related Continuation Application Prosecution

60. Using the same specification (written description) as the '847 patent, the Patent Owner submitted a continuation of the original '290 Application with an independent claim that was virtually identical to claim 1 the '847 patent. EX1006, 29. Following rejections by the patent office examiner in view of Bolli and Keyser, I understand that Patent Owner appealed to the Patent Trials and Appeals Board ("PTAB"), which includes administrative patent judges that handle appeals from patent examiner rejections (and that handles IPR proceedings). I understand that the PTAB reversed the examiner's rejection and said that the patent claims were allowable. *Id.*, 458-59. After that decision in Patent Owner's favor, I understand that Patent Owner abandoned (gave up on) the application.

61. In its arguments to the examiner and also before the PTAB on appeal of the examiner's rejection, it is my understanding that Patent Owner relied on a 2008 article by Iglarz *et al.* (EX1011) to argue that there was a surprising effect when combining a PDE5 inhibitor with the claimed ET_A receptor antagonist (the compound of formula (I), known as macitentan). *Id.*, 385. This is because, according to the Patent Owner, Keyser "teaches away" from using an ET_A receptor antagonist which also possesses ET_B activity and—because of this alleged "teaching away"—any synergy between such an ET_A receptor antagonist and a PDE5 inhibitor would

have been surprising. *Id.* The Patent Office accepted this argument and reversed the rejection, citing surprising, synergistic results. *Id.*, 463-65. The Patent Owner abandoned their application despite the successful result on appeal. *Id.*, 529.

3. '847 Patent Reexamination

62. Five years after the issuance of the '847 patent, the Patent Owner requested a reexamination of the '847 patent. In its reexamination application, Patent Owner asked the Patent Office to consider the Bolli reference that the examiner had originally excluded, combined with Keyser. EX1003, 304-306. Patent Owner submitted the appeal decision from the related application to argue that the claims were still nonobvious even if Bolli was considered. *Id.*, 289. The Patent Office accepted this reasoning and adopted the PTAB's reasoning in a Notice of Intent to Issue *Ex Parte* Reexamination Certificate. *Id.*, 375-76. In addition to the original first 11 claims, the reexamination certificate added claims 12-57 to the '847 patent. *Id.*, 380-390.

B. Patent Overview

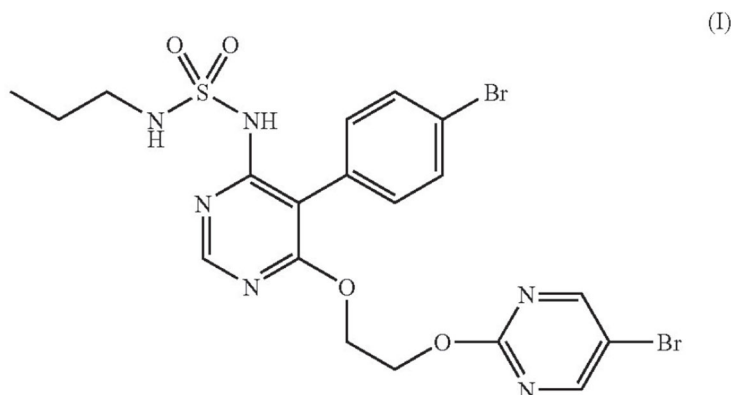
63. The '847 patent describes pharmaceutical compositions, including chemical structures, and methods for treating disorders related to blood flow, such as hypertension and PH, among other vascular conditions.

1. The Specification

a) Combination of Formula (I) and PDE5 Inhibitor.

64. The specification describes a combination of formula (I) with a

compound having PDE5-inhibitory properties. *See* EX1001, 1:16-38. The compound of formula (I), which is the chemical structural formula for macitentan, is provided below:



Id., 1:18-33; *see also id.*, 4:29-5:5.

65. The '847 patent defines a “compound having PDE5-inhibitory properties” as “a compound that . . . has an IC_{50} equal or lower than 1 μM .” *Id.*, 2:39-42; *see id.*, 6:10-50 (describing the test for the determination of PDE5 IC_{50}). The specification additionally provides “[s]pecific examples of compounds having PDE5-inhibitory properties” includes sildenafil, vardenafil, tadalafil, and udenafil (*id.*, 2:43-3:27, 3:58-60), and particularly preferably sildenafil or tadalafil (*see id.*, 3:60-67).

b) Dosage and Administration of Combination

66. The '847 patent defines administration of macitentan and a PDE5 inhibitor where the two drugs are administered simultaneously, separately, or over a

period of time to treat a disease involving vasoconstriction. *Id.*, 2:14-38, 3:36-57.

The '847 patent defines each of these terms (“simultaneously,” “separately,” and “over a period of time”) as follows:

“Simultaneously” or “simultaneous”, when referring to a therapeutic use, means in the present application that the therapeutic use concerned consists in the administration of two or more active ingredients by the same route and at the same time.

“Separately” or “separate”, when referring to a therapeutic use, means in the present application that the therapeutic use concerned consists in the administration of two or more active ingredients at approximately the same time by at least two different routes.

By therapeutic administration “over a period of time” is meant in the present application the administration of two or more ingredients at different times, and in particular an administration method according to which the entire administration of one of the active ingredients is completed before the administration of the other or others begins. In this way it is possible to administer one of the active ingredients for several months before administering the other active ingredient or ingredients. In this case, no simultaneous administration occurs.

Id., 2:14-34.

67. The '847 patent goes on to define administration routes of the claimed macitentan and PDE5 inhibitor combination and states a preference for delivering both drugs via the same administration route, which is preferably oral or intravenous with a particular emphasis on oral administration. *Id.*, 4:1-17. The '847 patent explains that “exact administration doses of [the claimed combination of macitentan and a PDE5 inhibitor] will have to be determined by the treating physician” but also discloses broad dosage ranges for macitentan, tadalafil, and sildenafil. *Id.*, 4:7-17. In

particular, the patent specification discloses macitentan dosage ranges of 0.05-2 mg per kilogram patient body weight (this unit is abbreviated hereinafter as “mg/kg”) or 0.1-1 mg/kg, tadalafil dosage ranges of 0.01-1 mg/kg or 0.05-0.5 mg/kg, and sildenafil dosage ranges of 0.1-2 mg/kg or 0.2-1 mg/kg. *Id.*, 4:7-17.

68. Vasoconstrictive disease states to be treated by the claimed products and compositions are disclosed in the patent specification as well: hypertension, PH, PAH, diabetic arteriopathy, heart failure, ED, and angina pectoris, with a particular emphasis on PH and PAH. *Id.*, 4:18-27.

c) Description of Prior Art

69. The '847 patent specification states that Bolli “describes endothelin receptor antagonists including the compound of formula (I) and the use of said endothelin receptor antagonists in the treatment of various diseases wherein vasoconstriction is involved (i.a. heart failure, angina pectoris, pulmonary and systemic hypertension and erectile dysfunction).” *Id.*, 1:39-44. Thus, the '847 patent admits that macitentan, the compound identified in claim 1, was known in the art and therefore not novel.

70. The '847 patent also explains that “PDE-5 inhibitors have been notably described” in at least four patents or patent publications. *Id.*, 1:45-59.

71. The only assertion of something new in the '847 patent is that the claims the applicant “surprisingly found that the combination of the compound of Formula

(I) with a compound having PDE-5 inhibitory properties results in an unexpected synergistic effect in the treatment of diseases wherein vasoconstriction is involved.”

Id., 1:60-64.

d) Examples 1-3

72. The '847 patent describes analysis of blood pressure responses to endothelin antagonism and PDE5 inhibition in two rodent animal models: the Dahl salt sensitive (“Dahl-S”) rat model and spontaneously hypertensive rat model (“SHR”). *Id.*, 5:15-25. As described in specification, Dahl-S rat models require hypertension to be induced by introducing salt to the daily diet. *Id.*, 5:38-39.

73. Examples 1-3 disclose the results of the test protocol. The table below summarizes the area between curves (“ABC”) results of each example:²

	Macitentan (0.3 mg/kg)	Tadalafil (10 mg/kg)	Sildenafil (30 mg/kg)	Macitentan (0.3 mg/kg) + Tadalafil (10 mg/kg)	Macitentan (0.3 mg/kg) + Sildenafil (30 mg/kg)
Example 1 (Dahl-S)	256	310	-	923	-
Example 2 (SHR)	44	286	-	444	-

² In all Examples, Formula (I) (“Form (I)”) is macitentan, administered orally at a dose of 0.3 mg/kg, tadalafil is administered orally at a dose of 10 mg/kg and sildenafil is administered orally at a dose of 30 mg/kg. EX1001, 5:15-25, Example 1-3.

Example 3 (SHR)	38	-	229	-	317
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74. As I explain in detail below, the POSA would not have found the data to show a surprising “synergistic result” because (1) the Examples omit important data, *e.g.*, sample size and variation; (2) the lack of control data; (3) the use of unconventional nomenclature and techniques; (4) the lack of dose-response data; and (5) the use of a 24-hour control period plotted against a 72-hour treatment period to find an ABC.

75. First, the Examples leave out important details, including the number of animals tested in each Example and the variation (*e.g.*, standard deviation) seen in the data collected from the rats. Without the number of animals in each study (the “n” value or sample size) or the standard deviation of the blood pressure area under the curve (“AUC”) or even ABC values, any calculations relating to the alleged synergy are fairly meaningless.

76. The ’847 patent does not provide the standard deviation of the blood pressure ABC values and does not include further statistical analysis, dose-response data, or control data (*e.g.*, control responses or that the data were modified and presented as a percentage of control).

77. I am familiar with the Dahl-S and SHR rats from my work in the industry. In Dahl-S rats, salt is added to the daily diet, but not all animals eat every bit of chow every day and the level of hypertension achieved in each animal varies.

The same can be said of the SHR rat model, as genes work differently in different individuals. The POSA would have understood that varying baselines (*i.e.*, starting points of hypertension) lead to variation in the purported results unless sufficient sample sizes and controls are used. But there is no evidence of that here. As I mention above, the '847 patent fails to provide even an “n” value indicating how many animals were tested. *See supra* §VI.B.1.d.

78. Second, the Examples used the rats as their own controls and there was no placebo control arm. In the protocol described in the '847 patent Examples, each rat served as its own control for 24 hours (blood pressure telemetry monitored), followed by oral dosing of test articles and analysis of blood pressure for another 72 hours at 5-minute intervals. *See id.*, 5:59-6:8. The specification does not provide the number of animals/groups studied. The ABC data does not show any control responses or that the data were modified and presented as a percent of control (which would be the normal convention for the POSA).

79. Third, the POSA would not have applied heavy weight to the data because it uses unconventional nomenclature and techniques. The ABC from 0-72 hours was calculated using two curves: blood pressure of the control period and blood pressure of the treatment period. *Id.* The specification reasons that “[t]he higher the ABC, the stronger the effect of the item tested for lowering blood pressure.” *Id.*, 6:1-3. But ABC is not industry standard, typically the POSA would

have looked at the AUC for each parameter.

80. Fourth, the '847 patent offers no dose-response data—*i.e.*, data obtained using different dosages of active ingredients—even though such data is critical in quantitating pharmacological data and the degree of efficacy and safety achievable. Without data resulting from varying the dosages of macitentan, tadalafil, and sildenafil, the POSA would not have interpreted the results presented as supporting the full breadth of the patent claims, let alone as showing surprising synergy because that would require extrapolating from a single data point, which is not statistically permissible. The patent does not disclose results obtained using different doses of macitentan or different doses of tadalafil or sildenafil. The POSA could not have reasonably extrapolated whether there is synergy across the full scope of the patent claims or form any reasonable expectations of synergy from only a single macitentan/tadalafil dosage combination or a single macitentan/sildenafil dosage combination. As explained below, the data provided in Examples 1-3 of the '847 patent do not support a finding of synergism across the claimed doses of macitentan, tadalafil, or sildenafil recited in any of claims 23-37 or claims 43-57, let alone for any of the other claims which are altogether silent as to dosages. *See infra* §VII.F.

81. Fifth, the '847 patent explains that “[e]ach rat served as its own control, by using the blood pressure data of the last 24 hours before drug administration” and

that curves for the treatment period and control period were plotted against each other to find the area between them (*i.e.*, ABC). EX1001, 5:63-6:9. However, the '847 patent makes clear that the treatment period was 72 hours. *Id.* It is unclear how a 24-hour control period was plotted against a 72-hour treatment period to find an ABC. The patent specification fails to provide the plotted curves or underlying data. Nor does the '847 patent provide any guidance as to how the control and treatment datasets—which differ on a timescale by a factor of *three*—were used to determine the ABC values reported in Examples 1-3. The POSA would not have had any basis to meaningfully interpret the underlying data (which is wholly absent from the patent disclosure) or the reported ABC values.

82. The data presented in Examples 1-3 of the '847 patent are thus insufficient to convey to the POSA that surprising synergism was in fact exhibited or observed.

2. '847 Patent Claims

83. The '847 patent claims are generally directed to the combination of an endothelin receptor antagonist and a PDE5 inhibitor. *See, e.g.*, EX1001, claim 1. The patent has 57 claims.

84. As described in Section VI.A above, claims 1-11 issued on September 18, 2012 and claims 12-57 later issued after reexamination on April 16, 2018. *Id.*, 1, 7.

85. The claims are directed to a product (claim 1-5), a pharmaceutical composition (claims 6-9), or a method of treatment (claims 10-57). *Id.*, 6, 8-9.

86. **Disease State Claims.** Certain claims are further directed to disease states involving vasoconstriction (claim 1), and more specifically hypertension, PH, diabetic arteriopathy, heart failure, ED, and angina pectoris (claim 5). *Id.*, 6. The claims are narrowed to the treatment of hypertension or PH (claims 10-13) and even further narrowed to the treatment of PH or PAH (claims 14-57). *Id.*, 6, 8-9.

87. **PDE5 Inhibitor Claims.** Certain claims are directed to specific PDE5 inhibitors. The PDE5 inhibitors claimed are sildenafil, vardenafil, tadalafil, and udenafil (claims 2, 7, 11) and further narrowed to tadalafil (claims 3, 8, 12) and sildenafil (claims 4, 9, 13). *Id.*, 6, 8. Additional claims related to dosing and administration further include limitations to tadalafil and sildenafil, *e.g.*, claims 18-21, 24, 27, 30, 33, 36, 38-41, 44, 47, 50, 53, 56. *Id.*, 8-9.

88. **Administration Claims.** The claims are also directed to the administration of macitentan and a PDE5 inhibitor simultaneously, separately, or over a period of time. *Id.*, 6. The claims are further narrowed to the administration of macitentan and tadalafil (claims 18-22) and sildenafil (claims 38-42) simultaneously, separately, or over a period of time. *Id.*, 8-9.

89. **Dosage Claims.** Additionally, there are several claimed dose ranges for macitentan. Dose ranges for macitentan claimed are between 0.05 mg to 2 mg per

kilogram of patient body weight (claims 23, 26, 29, 32, 35, 43, 46, 49, 52, 55) and further narrowed to 0.1 mg to 1 mg per kilogram of patient body weight (claims 25, 28, 31, 34, 37, 45, 48, 51, 54, 57). *Id.*, 8-9.

90. **Dose Range Claims.** The claims are also directed to dose ranges for tadalafil and sildenafil. Dose ranges for tadalafil claimed are between 0.01 mg to 1 mg per kilogram of patient body weight (claims 24, 27, 30, 33, and 36) and dose ranges for sildenafil claimed are between 0.1 mg to 2 mg per kilogram of patient body weight (claims 44, 47, 50, 53, and 56). *Id.*

VII. Anticipation and Obviousness Analysis

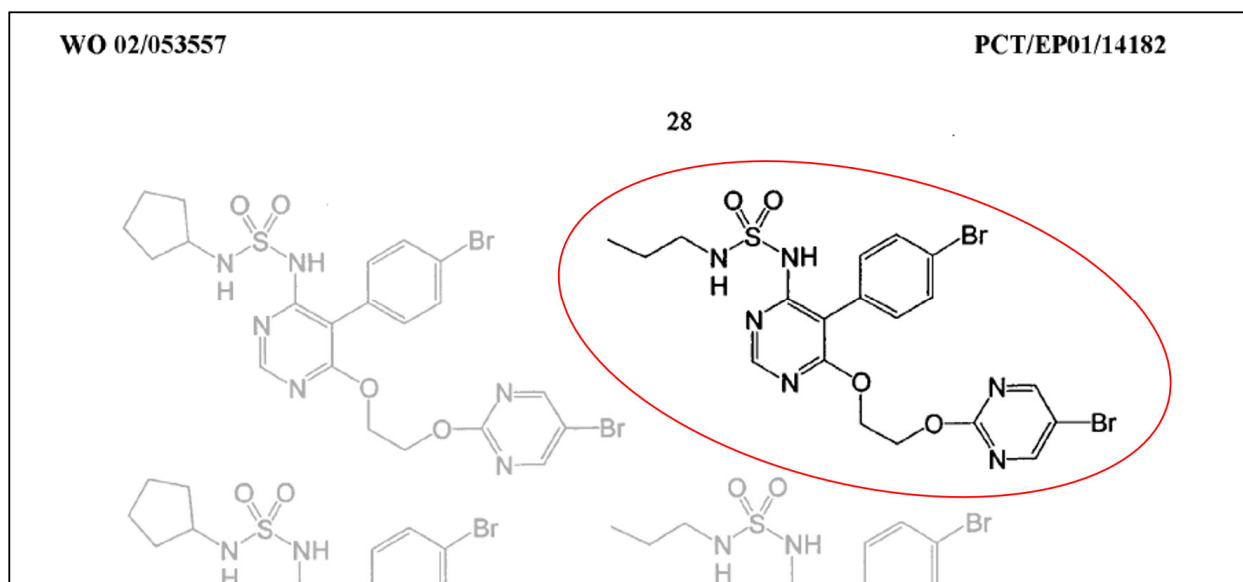
A. Anticipation by Bolli

91. Bolli discloses each of claims 1-57 either because Bolli literally discloses the claim limitations or because the POSA would have understood Bolli to disclose them.

92. Bolli discloses endothelin receptor antagonist compounds in combination with vasodilators, pharmaceutical compositions containing those compounds, and methods of treating diseases including hypertension and PH involving administration of those compounds and pharmaceutical compositions. EX1004, 12 (disclosing 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.”), 18 (teaching macitentan “in combination with ... vasodilators ... which serve to treat high blood pressure or any cardiac disorders.”).

93. Bolli expressly discloses the claimed compound of formula (I), macitentan. Specifically, Bolli teaches the chemical structure of macitentan and describes it as an “especially preferred” endothelin receptor antagonist. *See id.*, 22; *see also id.*, 25 (“Another group of preferred compounds is depicted below.”). The chemical structure for macitentan is shown on page 29 of Bolli:



Id., 29 (annotation added).

94. Due to heightened levels of ET-1 associated with various cardiovascular diseases and conditions, endothelin receptor antagonists have been the subject of considerable research to evaluate their effectiveness in treating

diseases involving vasoconstriction (*e.g.*, hypertension or PH) since the date of priority. *See e.g.*, EX1009, 1. The POSA knew that, as a drug class, endothelin receptor antagonists such as macitentan were useful in treating diseases involving vasoconstriction—*e.g.*, hypertension and PAH—by mediating the effects of ET-1 binding to endothelin receptors.

95. Bolli further explains that its compounds, including “preferred” compound macitentan, “may also be used in combination with one or more . . . vasodilators . . . which serve to treat high blood pressure or any cardiac disorders.” EX1004, 18. Bolli’s disclosure 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.” *Id.*, 12.

96. In the context of Bolli’s disclosure, which concerns treatments for, among other things, ED, in combination with knowledge of this particular field, the POSA understood that “vasodilators” includes sildenafil and tadalafil. The POSA knew sildenafil (Viagra®) and tadalafil (Cialis®) were blockbuster drugs specifically known and used in the relevant field as vasodilators and PDE5 inhibitors. At minimum, the POSA would have recognized macitentan with sildenafil or tadalafil in light of Bolli’s teaching of macitentan, “in combination with

... vasodilators ... which serve to treat high blood pressure or any cardiac disorders.” *Id.*, 18. Because sildenafil and tadalafil were blockbuster drugs, it would have been immediately apparent to the POSA in view of Bolli’s disclosure concerning vasodilators in the same field to use these PDE5 inhibitors with macitentan. No more than Bolli’s description with the POSA’s knowledge would have been necessary to possess, make, and implement the claimed invention.

97. The POSA also knew that sildenafil (Viagra®) and tadalafil (Cialis®) are two of a limited class of vasodilators and are blockbuster drugs known in the field. For example, sildenafil (Viagra®) and tadalafil (Cialis®) were approved by FDA in 1998 and 2003, respectively, for oral administration for ED therapy or treatment. *See* EX1007, 19; EX1008, 26. Widespread use and demonstrated safety and efficacy in treating ED led to the appearance of generic forms of both drugs on the market. Thus, the POSA would have understood Bolli’s use of the term “vasodilators” to include sildenafil and tadalafil when Bolli expressly describes its compounds and combinations as being useful for treating ED, hypertension, PH, and related diseases. *See* EX1004, 12 (“[T]he described compounds can be used 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.”).

98. Furthermore, the POSA also knew PDE5 inhibitors were the subject of considerable research efforts into developing new treatments for ED, hypertension, PH, and other diseases and conditions involving vasoconstriction. For example, a European patent application entitled “Treatment of pulmonary hypertension,” describes the use of PDE5 inhibitors such as sildenafil for treatment of PH, (EX1015, [57], [0001]-[0010], claims 1-20) including use of PDE5 inhibitors “administered together with . . . endothelin antagonists (ETa),” (*id.*, [0036]). With respect to PH, including PAH, the POSA would also have known that sildenafil was suggested as an additional therapeutic for PAH patients receiving endothelin receptor antagonists. *See, e.g.*, 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”). Additionally, the POSA would have known that sildenafil was also approved by FDA in 2005 for PAH treatment under the brand name Revatio®. EX1025.

99. As evidenced by the POSA’s knowledge of the hugely commercially successful vasodilator PDE5 inhibitors tadalafil and sildenafil, the POSA would have understood Bolli fully and effectively describes the claims of the ’847 patent that combine macitentan with sildenafil or tadalafil for the treatment of a disease wherein vasoconstriction is involved. *Infra* §VII.A.1. Therefore, the POSA would have understood that Bolli discloses the ’847 patent’s combination of macitentan

and PDE5 inhibitors sildenafil (Viagra®) and tadalafil (Cialis®).

1. Product claims 1-5

100. For the reasons I explain below, Bolli anticipates claims 1-5.

a) Claim 1

101. Independent claim 1 recites:

Claim 1	
[1.Pre]	1. A product containing
[1.1]	the compound of formula (I)³ 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.

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

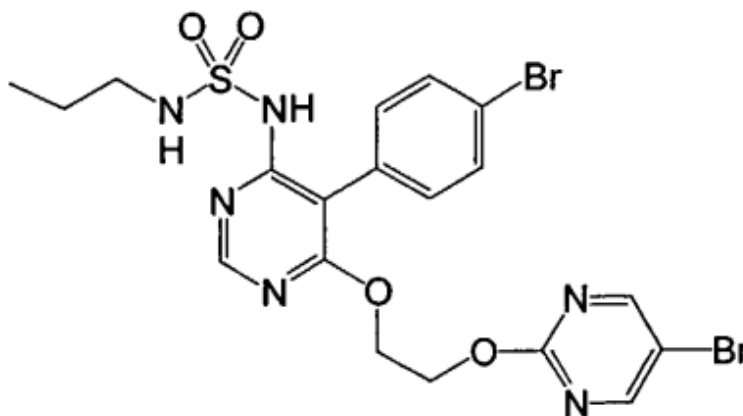
102. Bolli describes “pharmaceutical compositions containing one or more compounds of the general formula I and especially their use as endothelin receptor antagonists.” EX1004, 2. Pharmaceutical compositions with pharmaceutical active ingredients meet the “product” limitation of claim 1. Bolli thus discloses a “product”

³ The “compound of formula (I)” drawn in claim 1 of the ’847 patent is macitentan.

as recited in claim 1.

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

103. Bolli expressly discloses the claimed compound of formula (I)—*i.e.*, macitentan—on page 29:



Id., 29 (right column, first/top-listed structure).

104. Additionally, claim 11 of Bolli recites specific species of Bolli’s formula I, including “[p]ropylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-bromopyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide,” which is macitentan. *Id.*, 135 (claim 11).

105. Bolli also describes macitentan as a compound according to Bolli’s formula V, which defines an “especially preferred group of compounds.” *Id.*, 22.

106. Bolli further discloses that macitentan can be in free or pharmaceutically acceptable salt form. *Id.*, 13-15 (“The present invention relates to pyrimidine-sulfamides of the general formula I . . . and pharmaceutically acceptable

salts thereof.”). The ’847 patent defines “pharmaceutically acceptable salt” as “non-toxic, inorganic or organic acid and/or base addition salts.” EX1001, 3:28-31. The patent’s definition aligns with Bolli’s definition for “pharmaceutically acceptable salts” (“The expression pharmaceutically acceptable salts encompasses either salts with inorganic acids or organic acids like hydrohalogenic acids, e.g. hydrochloric or hydrobromic acid; sulfuric acid, phosphoric acid, nitric acid, citric acid, formic acid, acetic acid, maleic acid, tartaric acid, methanesulfonic acid, p- toluenesulfonic acid and the like or in case the compound of formula I is acidic in nature with an inorganic base like an alkali or earth alkali base, e.g. sodium hydroxide, potassium hydroxide, calcium hydroxide and the like.”). *See* EX1004, 16.

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

107. Claim 1 further requires that macitentan is provided in combination with at least one compound having PDE5-inhibitory properties, in free or a pharmaceutically acceptable salt form. EX1001, claim 1. Bolli discloses this combination of active ingredients, as it would have been immediately apparent to the POSA based on Bolli’s disclosure.

108. Bolli discloses macitentan as a preferred compound according to Bolli’s invention, and that Bolli’s compounds “may also be used in combination with

one or more other therapeutically useful substances e.g. . . . vasodilators[.]” EX1004, 18.

109. As I explain above, combining macitentan with a PDE5 inhibitor, such as sildenafil or tadalafil, would have been immediately apparent to the POSA. *Supra* §VII.A, ¶¶ 92-99. Sildenafil and tadalafil were both widely known, commercially successful vasodilators known to be effective for treating ED, among other diseases involving vasoconstriction. *See id.* Therefore, Bolli discloses the claimed combination of macitentan and at least one PDE5 inhibitor.

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

110. Bolli also discloses use of the combination of macitentan with vasodilators “for therapeutic use, simultaneously, separately[,] or over a period of time, in the treatment of a disease wherein vasoconstriction is involved.”

111. The ’847 patent broadly defines diseases “wherein vasoconstriction is involved” to include “hypertension, pulmonary hypertension (including pulmonary arterial hypertension), diabetic arteriopathy, heart failure, erectile dysfunction or angina pectoris.” EX1001, 2:36-39. Bolli discloses that its compounds, including macitentan, “mediate[] vasoconstricting and proliferative responses.” EX1004, 2. Additionally, Bolli discloses that “[e]ndothelin receptor antagonists have demonstrated preclinical and/or clinical efficacy in . . . pulmonary and systemic

hypertension.” *Id.*, 3; *see also id.*, 12 (“[T]he described compounds can be used 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.”); *id.*, claims 12, 14, and 18. Thus, Bolli teaches use of these compounds for therapeutic use treating a disease where vasoconstriction is involved.

112. Bolli also teaches use “simultaneously, separately[,] or over a period of time.” *Supra* §VI.B.1.b. The ’847 patent defines “simultaneously” and “simultaneous,” “separately” or “separate,” and “over a period of time” as follows:

“Simultaneously” or “simultaneous”, when referring to a therapeutic use, means in the present application that the therapeutic use concerned consists in the administration of two or more active ingredients by the same route and at the same time.

“Separately” or “separate”, when referring to a therapeutic use, means in the present application that the therapeutic use concerned consists in the administration of two or more active ingredients at approximately the same time by at least two different routes.

By therapeutic administration “over a period of time” is meant in the present application the administration of two or more ingredients at different times, and in particular an administration method according to which the entire administration of one of the active ingredients is completed before the administration of the other or others begins. In this way it is possible to administer one of the active ingredients for several months before administering the other active ingredient or ingredients. In this case, no simultaneous administration occurs.

EX1001, 2:14-35.

113. Additionally, as I explain in greater detail below with respect to claims

18-22 and 38-42 of the '847 patent, Bolli teaches various routes of administration of macitentan, and the POSA knew sildenafil (Viagra®) and tadalafil (Cialis®) to be commercially available in their FDA-approved oral dosage forms. *See infra*, §VII.A.3.d. Hence, co-administration of an oral PDE5 inhibitor (*e.g.*, sildenafil or tadalafil) and macitentan by *any* of the routes disclosed by Bolli—rectally, parenterally (*e.g.*, intravenously, intramuscularly, subcutaneously, intrathecally, transdermally) sublingually, or via ophthalmic or aerosol preparations—would meet the claimed simultaneous or separate administration limitations of the '847 patent claims in accordance with how the patent specification defines those terms. *See* EX1004, 12.

114. Bolli also teaches administration of macitentan and a PDE5 inhibitor “over a period of time” as that term is defined in the '847 patent. The POSA would have immediately understood Bolli’s disclosure of combinations of macitentan and sildenafil or tadalafil to include administration of macitentan and either sildenafil or tadalafil at different times such that administration of one of the drugs is completed before administration of the other. *See* EX1001, 2:25-35. The broad definition for administration “over a period of time” provided by the '847 patent includes administration of a first active ingredient “for several months before administering the other active ingredient or ingredients” such that “no simultaneous administration occurs.” *See id.* The POSA would have understood Bolli to disclose administration

of two drugs which are performed according to wholly distinct dosing regimens.

115. The '847 patent appears to try to encompass administration of macitentan and a PDE5 inhibitor according to all conceivable timings and administration routes, each of which is taught by Bolli. Indeed, Actelion acknowledges in the '847 patent itself that each claimed administration timing was fully within the POSA's knowledge and capabilities. *See* EX1001, 4:7-9 ("the exact administration doses . . . will have to be determined by the treating physician.").

116. Thus, the POSA would have understood that the combination disclosed in Bolli would include administration of the two drugs "simultaneously," "separately," and "over a period of time."

117. Accordingly, Bolli anticipates claim 1 of the '847 patent.

b) Claims 2-4

118. Claims 2-4 recite:

2. The product according to claim 1, wherein the compound having PDE5-inhibitory properties is selected from sildenafil, vardenafil, tadalafil and udenafil.
3. The product according to claim 2, wherein the compound having PDE5-inhibitory properties is tadalafil.
4. The product according to claim 2, wherein the compound having PDE5-inhibitory properties is sildenafil.

119. As I explain above with respect to claim 1, it would have been immediately apparent to the POSA to combine macitentan with sildenafil or tadalafil

for the reasons described above regarding claim 1. *Supra* §VII.A, ¶¶ 92-99; §VII.A.1.a.3, ¶¶ 108-09. Accordingly, Bolli anticipates claims 2-4 of the '847 patent.

c) Claim 5

120. Claim 5 recites:

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.

121. Bolli discloses the limitation in claim 5. *E.g.*, EX1004, 3 (“Endothelin receptor antagonists have demonstrated preclinical and/or clinical efficacy in various diseases such as cerebral vasospasm following subarachnoid hemorrhage, heart failure, pulmonary and systemic hypertension, neurogenic inflammation, renal failure and myocardial infarction.”); *id.*, 12 (“[T]he described compounds can be used for treatment of ... hypertension, pulmonary hypertension, [and] erectile dysfunction”).

122. As I explain above with respect to claim 1, it would have been immediately apparent to the POSA to combine macitentan with a PDE5 inhibitor to treat a disease involving vasoconstriction—including one or more of hypertension, PH, diabetic arteriopathy, heart failure, ED or angina pectoris. *See supra* §VII.A.1.a.4; EX1004, 3, 12.

123. The POSA would also know that PDE5 inhibitors such as sildenafil and

tadalafil were initially developed and intended as treatments for hypertension and PH, among other cardiovascular diseases. EX1033, 1. Although sildenafil (Viagra®) and tadalafil (Cialis®) were approved by the Food and Drug Administration as treatments for ED, research into their usefulness as cardiovascular medications continued. For example, numerous studies on sildenafil and tadalafil as potential treatments for PAH were published as of the priority date. *See e.g.*, EX1016, 5 (noting that sildenafil is a “potent and selective” PDE5 inhibitor that has been used in PH patients); EX1017, 1 (asserting that sildenafil has been “investigated for the treatment of pulmonary hypertension in both pediatric and adult patients.”); EX1018, 1 (“Increasing evidence has shown that sildenafil is an effective pulmonary vasodilator for both children and adults with primary pulmonary hypertension.”); EX1019, 6 (reporting “remarkabl[e]” improvement of PAH in a patient upon taking tadalafil); EX1020, 1 (noting the use of PDE5 inhibitors, specifically sildenafil and tadalafil, as treatment options for cardiovascular diseases like hypertension); EX1021, 2 (reporting recent studies that indicate sildenafil as improving primary PH symptoms); EX1022, 1 (noting that sildenafil is an effective pulmonary vasodilator that has shown symptom improvement in patients with PH).

124. Sildenafil and tadalafil were two PDE5 inhibitors that were clear candidates for PH or PAH, as they had already shown promise in the PH field. *See* EX1007; 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 that sildenafil was suggested as an additional therapeutic for PAH patients receiving endothelin receptor antagonists. *See, e.g.*, 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 that the citrate salt of sildenafil was approved for treatment of PAH in 2005 under the brand name Revatio®. *See* EX1025.

125. Thus, the POSA would have immediately understood that PDE5 inhibitors such as tadalafil and sildenafil were vasodilators for treating hypertension and PH (*e.g.*, PAH) and not only ED.

126. Accordingly, Bolli anticipates claim 5 of the ’847 patent.

2. Pharmaceutical composition claims 6-9

127. Bolli also anticipates the pharmaceutical composition claims (*i.e.*, claims 6-9) of the ’847 patent.

a) Claim 6

128. Claim 6 recites:

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.

129. Claim 6 recites a “pharmaceutical composition” containing the compound of formula (I) recited in claim 1 (macitentan) and a PDE5 inhibitor as “active principles” along with “at least one excipient.” EX1001, claim 6.

130. Bolli discloses the use of macitentan and vasodilators as active pharmaceutical ingredients in combination, and using a PDE5 inhibitor, such as sildenafil or tadalafil, as vasodilators in those combinations would have been immediately apparent to the POSA, as I explain above with respect to claim 1. *Supra* §VII.A, ¶¶ 92-99; §VII.A.1.a.3, ¶¶ 108-09. Bolli further discloses using at least one excipient, stating that “[t]he preparations with compounds can contain inert or as well pharmacodynamically active excipients. Tablets or granules, for example, could contain a number of binding agents, filling excipients, carrier substances or diluents.” See EX1004, 12; *see also id.*, 17-18, claims 12-13, 20. The POSA would also have known that drugs can be formulated with an excipient (or multiple) for various reasons, including to add preservatives, make the drug more readily usable for the specific route of administration, etc. 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

131. Accordingly, Bolli anticipates claim 6 of the '847 patent.

b) Claims 7-9

132. Claims 7-9 recite:

7. The pharmaceutical composition according to claim 6, wherein the compound having PDE5-inhibitory properties is selected from sildenafil, vardenafil, tadalafil and udenafil.

8. The pharmaceutical composition according to claim 7, wherein the compound having PDE5-inhibitory properties is tadalafil.

9. The pharmaceutical composition according to claim 7, wherein the compound having PDE5-inhibitory properties is sildenafil.

133. As I explain above with respect to claims 1 and 6, Bolli discloses macitentan in combination with vasodilators and using a PDE5 inhibitor, including sildenafil and tadalafil, would have been immediately apparent to the POSA. *Supra* §VII.A, ¶¶ 92-99; §VII.A.1.a.3, ¶¶ 108-09; §VII.A.2.a. Accordingly, Bolli anticipates claims 7-9 of the '847 patent.

3. Method of treatment claims 10-57

134. Bolli also anticipates the method of treatment claims (*i.e.*, claims 10-57) of the '847 patent.

a) Claim 10

135. Claim 10 recites:

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.

136. As I explain above, Bolli discloses macitentan in combination with vasodilators and using a PDE5 inhibitor, including sildenafil and tadalafil, would have been immediately apparent to the POSA. *Supra* §VII.A, ¶¶ 92-99; §VII.A.1.a.3, ¶¶ 108-09. The POSA would have understood that the reason to use the combination disclosed in Bolli is in a method of treating patients. For example, Bolli discloses a “method for the treatment of hypertension or pulmonary hypertension.” *See, e.g.*, EX1004, 3 (“Endothelin receptor antagonists have demonstrated preclinical and/or clinical efficacy in . . . pulmonary and systemic hypertension”); *id.*, 12 (“Because of their ability to inhibit the endothelin binding, the described compounds can be used for treatment of diseases, which are associated with an increase in vasoconstriction, proliferation or inflammation due to endothelin. Examples of such diseases are hypertension, pulmonary hypertension”); *see also id.*, claims 12, 14, and 18.

137. Additionally, as I explain above, the POSA would have known that PDE5 inhibitors such as sildenafil and tadalafil were initially developed and intended as treatments for hypertension and PH, among other cardiovascular diseases. *See supra* §VII.A.1.c; *see* EX1033, 1. Although sildenafil (Viagra®) and

tadalafil (Cialis®) were approved by the Food and Drug Administration as treatments for ED, research into their usefulness as cardiovascular medications continued. For example, numerous studies on sildenafil and tadalafil as potential treatments for PAH were published as of the priority date. *See e.g.*, EX1016, 5 (noting that sildenafil is a “potent and selective” PDE5 inhibitor that has been used in PH patients); EX1017, 1 (asserting that sildenafil has been “investigated for the treatment of pulmonary hypertension in both pediatric and adult patients.”); EX1018, 1 (“Increasing evidence has shown that sildenafil is an effective pulmonary vasodilator for both children and adults with primary pulmonary hypertension.”); EX1019, 6 (reporting “remarkabl[e]” improvement of PAH in a patient upon taking tadalafil); EX1020, 1 (noting the use of PDE5 inhibitors, specifically sildenafil and tadalafil, as treatment options for cardiovascular diseases like hypertension); EX1021, 2 (reporting recent studies that indicate sildenafil as improving primary PH symptoms); EX1022, 1 (noting that sildenafil is an effective pulmonary vasodilator that has shown symptom improvement in patients with PH).

138. As I explain above, sildenafil and tadalafil were two PDE5 inhibitors that were clear candidates for PH or PAH, as they had already shown promise in the PH field. *See supra* §VII.A.1.c; *see also* EX1007; 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 PH). The POSA would also have known that sildenafil was suggested as an additional therapeutic for PAH patients receiving endothelin receptor antagonists. *See, e.g.*, 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 that the citrate salt of sildenafil was approved for treatment of PAH in 2005 under the brand name Revatio®. *See* EX1025.

139. Thus, the POSA would have immediately understood that PDE5 inhibitors such as tadalafil and sildenafil were vasodilators for treating hypertension and PH (*e.g.*, PAH) and not only ED.

140. Accordingly, Bolli anticipates claim 10 of the '847 patent.

b) Claims 11-13

141. Claims 11-13 recite:

11. The method according to claim 10, wherein the compound having PDE5-inhibitory properties is selected from sildenafil, vardenafil, tadalafil and udenafil.

12. The method of claim 11, wherein the compound having PDE5-inhibitory properties is tadalafil.

13. The method of claim 11, wherein the compound having PDE5 inhibitory properties is sildenafil.

142. As I explain above with respect to claim 1 and dependent claims 2-4,

and claim 10, the features of claims 11-13 would have been readily apparent to the POSA based on Bolli's disclosure. *Supra* §VII.A, ¶¶ 92-99 (describing Bolli's disclosure of the use of macitentan in combination with vasodilators, which the POSA would have immediately understood to include tadalafil and sildenafil); §VII.A.1.a.3 (anticipation of claim limitation 1.2 "in combination with at least one compound having PDE5-inhibitory properties, in free or a pharmaceutically acceptable salt form"); §VII.A.1.b (anticipation of claims 2-4); §VII.A.3.a (anticipation of claim 10). As explained above, Bolli discloses macitentan combined with vasodilators and using a PDE5 inhibitor, including sildenafil and tadalafil, would have been immediately apparent to the POSA. Accordingly, Bolli anticipates claims 11-13 of the '847 patent.

c) Claims 14-17

143. Claims 14-17 recite:

14. The method of claim 12, wherein the method is for the treatment of pulmonary hypertension.

15. The method of claim 14, wherein the pulmonary hypertension is pulmonary arterial hypertension.

16. The method of claim 13, wherein the method is for the treatment of pulmonary hypertension.

17. The method of claim 16, wherein the pulmonary hypertension is pulmonary arterial hypertension.

144. Claims 14-17 depend from claims 12 or 13 and additionally require treating PH or PAH.

145. As explained above, Bolli discloses macitentan in combination with vasodilators and using a PDE5 inhibitor, including sildenafil and tadalafil, would have been immediately apparent to the POSA. *Supra* §VII.A, ¶¶ 92-99; §VII.A.1.a.3, ¶¶ 108-09. Bolli also discloses, as discussed above regarding claim 5, that ET receptor antagonists such as macitentan can treat “pulmonary and systemic hypertension.” *Supra* §VII.A.1.c; *see, e.g.*, EX1004, 3 (“Endothelin receptor antagonists have demonstrated preclinical and/or clinical efficacy in . . . pulmonary and systemic hypertension.”).

146. The POSA also knew that, as of the presumed August 2006 priority date, sildenafil had been approved not only for treatment of ED under the brand name Viagra®, but also for PAH under the brand name Revatio®. *See* EX1025.

147. Furthermore, as of the presumed priority date, the POSA would have known PDE5 inhibitors such as sildenafil and tadalafil were the subjects of considerable research efforts into developing new treatments for, among other vasoconstrictive diseases, PH and PAH. *See, e.g.*, EX1009, 1 (noting that PDE5 inhibitors, such as sildenafil, may have beneficial effects in PAH); EX1010, 1 (finding that sildenafil and tadalafil improved the symptoms of a patient with PH); *e.g.*, EX1015, [57], [0001]-[0010], [0036] (documenting the use of PDE5 inhibitors, particularly sildenafil, for the treatment of PH); EX1016, 5 (finding that sildenafil is a “potent and selective” PDE5 inhibitor for treatment of PH patients); EX1017, 1

(stating that sildenafil has been “investigated for the treatment of pulmonary hypertension in both pediatric and adult patients.”); EX1018, 1 (“Increasing evidence has shown that sildenafil is an effective pulmonary vasodilator for both children and adults with primary pulmonary hypertension.”); EX1019, 6 (asserting “remarkabl[e]” improvement of PAH symptoms in a patient upon taking tadalafil); EX1020, 1 (noting the use of PDE5 inhibitors, specifically sildenafil and tadalafil, as treatment options for cardiovascular diseases like hypertension); EX1021, 2 (reporting recent studies that indicate sildenafil as improving primary PH symptoms); EX1022, 1 (noting that sildenafil is an effective pulmonary vasodilator that has shown symptom improvement in patients with PH); EX1025, 1 (prescribing the citrate salt of sildenafil for treatment of PAH).

148. Thus, it would have been immediately apparent to the POSA to administer the macitentan and sildenafil and/or macitentan and tadalafil combinations disclosed by Bolli for the treatment of PH (based on express disclosure) and PAH. Thus, Bolli anticipates claims 14-17.

d) Claims 18-22 and 38-42

149. Claims 18-22 and 38-42 recite:

18. The method of claim 15, wherein the compound of formula (I) and tadalafil are administered simultaneously.

19. The method of claim 15, wherein the compound of formula (I) and tadalafil are administered separately.

20. The method of claim 15, wherein the compound of formula (I) and

tadalafil are administered over a period of time.

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.

22. The method of claim 21, wherein the interval does not exceed one day.

38. The method of claim 17, wherein the compound of formula (I) and sildenafil are administered simultaneously.

39. The method of claim 17, wherein the compound of formula (I) and sildenafil are administered separately.

40. The method of claim 17, wherein the compound of formula (I) and sildenafil are administered over a period of time.

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.

42. The method of claim 41, wherein the interval does not exceed one day.

(1) Claims 18 and 38

150. I understand from the '847 patent that “simultaneously” means that two drugs are to be administered by the same administration route and at the same time. *See* EX1001, 2:15-19. Bolli discloses that macitentan is suitable for oral administration. *See* EX1004, 12 (“The compounds can be administered orally []. Examples of applications are capsules, tablets, [and] orally administered suspensions or solutions[.]”). Hence, an orally administered macitentan dosage form and a commercially available tadalafil tablet (*e.g.*, Cialis®) or sildenafil tablet (*e.g.*,

Viagra®) would be administered via the same administration route (*i.e.*, orally). *See* EX1008, 2. Bolli also teaches, for example, that “[t]he dosage should be administered preferably in 1 to 3 doses per day which are of equal weight.” EX1004, 18. The POSA would have known that the PDE5 inhibitor, such as sildenafil or tadalafil, could also be administered at least 1-3 times per day, and therefore also that oral administration of both active agents could be performed at the same time based on Bolli’s disclosure for, *e.g.*, patient compliance and convenience. EX1041, 1-3 (using sildenafil to treat patients with PAH administering 20, 40, or 80 mg sildenafil 3 times daily for 12 weeks); EX1042, 1-2 (using tadalafil to treat moderate PAH administering a daily dose of 20 mg every second day for six months). The POSA would have immediately understood that, of the options for administering two drugs, one of them is at the same time. Thus, Bolli anticipates claims 18 and 38 of the ’847 patent. *See e.g.*, EX1010, 1 (noting that a PDE5 inhibitor like sildenafil or tadalafil can be used to treat PAH and reporting a case study where 20 mg of tadalafil was substituted for 25 mg of sildenafil after patient compliance issues).

151. I further note that I did not see any assertion in the ’847 patent or its file history asserting that there is anything novel about simultaneous administration.

(2) Claims 19 and 39

152. I understand from the ’847 patent that “separately” means that the two drugs are to be administered by different routes of administration and at

approximately the same time. *See* EX1001, 2:20-24. Bolli discloses that, in addition to oral administration, macitentan can be administered “rectally, parenterally, e.g. by intravenous, intramuscular, subcutaneous, intrathecal or transdermal administration or sublingually or as ophthalmic preparation or administered as aerosol.” *See* EX1004, 12. Hence, any of the aforementioned administration routes for macitentan, in combination with a commercially available tadalafil or sildenafil tablet (e.g., Cialis®, Viagra®) would be administered via different administration routes (*i.e.*, separately). As explained above with respect to claims 18 and 38, it would have been immediately apparent to the POSA to administer both drugs at approximately the same time for, e.g., convenience or patient compliance. Accordingly, Bolli anticipates claim 19 of the ’847 patent.

153. I further note that I did not see any assertion in the ’847 patent or its file history asserting that there is anything novel about separate administration.

(3) Claims 20 and 40

154. I understand from the ’847 patent that “over a period of time” means that, irrespective of the administration routes used, macitentan and tadalafil (claim 20) or macitentan and sildenafil (claim 40) are to be administered at different times. *See* EX1001, 2:25-34. The POSA knew sildenafil (Viagra®) and tadalafil (Cialis®) to be commercially available in their FDA-approved oral dosage forms. *See* EX1008, 2. As I explain above, the POSA would have understood from Bolli that

administration of macitentan and a PDE5 inhibitor such as tadalafil or sildenafil over a period of time, which can include, according to the '847 patent itself, administration of one of the two active ingredients occurs for “months” followed by administration of the other. *See supra* §VII.A, ¶¶ 92-99 (describing Bolli’s disclosure of the use of macitentan in combination with vasodilators, which the POSA would have immediately understood to include tadalafil and sildenafil); §VII.A.1.a.3 (anticipation of claim limitation 1.2 “in combination with at least one compound having PDE5-inhibitory properties, in free or a pharmaceutically acceptable salt form”); §VII.A.1.a.4 (anticipation of claim limitation 1.3 “for therapeutic use, simultaneously, separately or over a period of time, in the treatment of a disease wherein vasoconstriction is involved”); EX1001, 2:25-35 (defining “over a period of time” to include administration of one of the active ingredients “for several months before administering the other active ingredient or ingredients.”).

155. I further understand that claims 20 and 40 encompass treatment of a patient with one of the two claimed drugs (*i.e.*, macitentan or the PDE5 inhibitor) followed by treatment with the other claimed drug such that “the entire administration of one of the active ingredients is completed before the administration of the other or others begins.” EX1001, 2:25-35. Such a treatment method includes treatment where the patient receives only, *e.g.*, macitentan and then at some indeterminate time later—which is unspecified by the claims and can be on the order

of days, weeks, months or even years—receives tadalafil or sildenafil.

156. I further note that I did not see any assertion in the '847 patent or its file history asserting that there is anything novel about simultaneous administration.

157. Moreover, as I explain above, Actelion itself acknowledges that each claimed administration timing—including administration “over a period of time”—is fully within the POSA’s knowledge and capabilities and, in fact, must be determined for each patient. *See* EX1001, 4:7-9 (“the exact administration doses. . . will have to be determined by the treating physician.”). The POSA would have understood Bolli’s disclosure to encompass administration of macitentan and tadalafil or sildenafil at different times because one of the few options for administering drug combinations is to start with one, monitor for side effects, and then introduce the other. A one-week period on one drug before starting the other would meet the “over a period of time” limitation and thus the POSA would have immediately understood administration of Bolli’s drug combinations to include administration of macitentan and either tadalafil or sildenafil over a period of time.

158. In determining a dosing regimen, the POSA would also have understood that different drugs can have different absorption, distribution metabolism, excretion (“ADME”) characteristics. Here, for example, tadalafil has a $T_{\max}$ (time to peak concentration in blood plasma) of 2 hours after oral dosing and half-life of 17.5 hrs. EX1037, 5. The difference in time to maximum plasma blood

levels between two drugs intended to be used in combination in patients will dictate the dosing regimen as it is the pharmacological intent for both drugs to peak in plasma at approximately the same time to have the maximal synergistic effect on the endpoint, in this case pulmonary or arterial blood pressure. Thus, any delay in macitentan to achieve maximal blood levels compared to tadalafil would warrant administering the macitentan first followed later by tadalafil administered “over a period of time” with the intent to maximize plasma drug levels temporally for both drugs concurrently.

159. I further note that I did not see any assertion in the '847 patent or its file history asserting that there is anything novel about administration over a period of time.

160. Accordingly, Bolli anticipates claims 20 and 40 of the '847 patent.

(4) Claims 21-22 and 41-42

161. Bolli discloses that “[i]n general the dosage [of macitentan] given daily in oral form should be between about 3 mg and about 3 g,” and “[t]he dosage should be administered preferably in 1 to 3 doses per day which are of equal weight.” EX1004, 18. The POSA would have known how to dose the commonly prescribed, commercially available tadalafil products Cialis® and Viagra®, including daily doses for PH and PAH. Administration of both macitentan and tadalafil on a daily basis at different times of day would thus fall within the scope of both claims 21 and

22.

162. Further, if the POSA were to prescribe PDE5s on an as-needed basis, daily administration of macitentan with any administered tadalafil would necessarily involve an interval of less than one day. Thus, any dosing regimen of tadalafil with a daily administration of macitentan as disclosed by Bolli would involve administration of both active ingredients at an interval not exceeding one day, let alone two days.

163. Additionally, as I explain above, Bolli teaches administration of macitentan and a PDE5 inhibitor such as tadalafil and sildenafil over a period of time, which can include, according to the '847 patent itself, administration of the two active ingredients which do not overlap in timing. *See supra* §VII.A, ¶¶ 92-99 (describing Bolli's disclosure of the use of macitentan in combination with vasodilators, which the POSA would have immediately understood to include tadalafil and sildenafil); §VII.A.1.a.3 (anticipation of claim limitation 1.2 "in combination with at least one compound having PDE5-inhibitory properties, in free or a pharmaceutically acceptable salt form"); §VII.A.1.a.4 (anticipation of claim limitation 1.3 "for therapeutic use, simultaneously, separately or over a period of time, in the treatment of a disease wherein vasoconstriction is involved"); §VII.A.3.d; *see* EX1001, 2:25-35. The POSA would have understood Bolli's methods of administering drug combinations to include administration of a PDE5

inhibitor which begins less than two days or less than one day after completion of a macitentan dosing regimen, or vice-versa where the PDE5 inhibitor is administered first followed by the macitentan. As I explain above, Actelion itself acknowledges that each claimed administration timing—including administration “over a period of time”—is fully within the POSA’s inherent knowledge and capabilities. *See* EX1001, 4:7-9 (“the exact administration doses . . . will have to be determined by the treating physician.”).

e) Claims 23-37 and 43-57

(1) Macitentan dosage claims 23, 25, 26, 28, 29, 31, 32, 34, 35, 37, 43 45, 46, 48, 49, 51, 52, 54, 55, and 57

164. Claims 23, 25, 26, 28, 29, 31, 32, 34, 35, 37, 43, 45, 46, 48, 49, 51, 52, 54, 55, and 57 recite:

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

165. Bolli describes administration of macitentan in a range of “dosages of 0.1-50 mg / kg body weight per day,” which substantially overlaps the claimed range of 0.05 mg to 2 mg per kilogram of patient body weight and encompasses the entire claimed range of 0.1 mg to 1 mg per kilogram of patient body weight. *See* EX1004, 12. Bolli goes on to also teach the overlapping macitentan dosage ranges of “between about 3 mg and about 3 g, preferably between about 10 mg and about 1 g, especially preferred between 5 mg and 300 mg, per adult with a body weight of about 70 kg.” *Id.*, 18. The POSA would have understood, by simply dividing these doses by the 70 kg mass (“body weight”) that 3 mg for a 70 kg adult is about 0.04 mg/kg body weight and that 3 g is 3,000 mg, which is about 43 mg/kg body weight. Likewise, 10 mg to 1 g (1,000 mg) is a range of 0.14-14 mg/kg body weight, and 5-300 mg is a range of

0.07-4.3 mg/kg body weight. Bolli therefore discloses the claimed dose ranges. Bolli also discloses the parent claims to these dependent claims as described above. Therefore, Bolli anticipates each of these claims.

(2) PDE5 inhibitor dosage claims 24, 27, 30, 33, 36, 44, 47, 50, 53, and 56

166. Claims 24, 27, 30, 33, 36, 44, 47, 50, 53, and 56 recite:

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

167. These claims therefore add limitations, to varying parent claims (claims

that they depend on) where either tadalafil is administered in a dose of 0.01-1 mg/kg body weight or sildenafil is administered in a dose of 0.1-2 mg/kg body weight. Bolli discloses a standard patient body weight for purposes of determining doses in the context of Bolli's disclosed products and methods for treating vasoconstriction-related diseases (*e.g.*, ED, hypertension, PH, and the like) of 70 kg. EX1004, 18.

168. ***Tadalafil.*** Claims 24, 27, 30, 33, and 36 recite a dose range for tadalafil of 0.01 mg to 1 mg per kilogram of patient body weight.

169. Tadalafil was approved in three oral dosage forms: 5 mg, 10 mg, and 20 mg tablets. *See* EX1008, 2. Using a patient body weight of 70 kg, any of the commercially available dosages of tadalafil (*e.g.*, Cialis® tablets) of 5 mg, 10 mg, or 20 mg would fall within the scope of claims 24, 27, 30, 33, and 36, as shown by the below calculations:

$$5 \text{ mg tadalafil} \div 70 \text{ kg body weight} = 0.071 \text{ mg/kg body weight}$$

$$10 \text{ mg tadalafil} \div 70 \text{ kg body weight} = 0.14 \text{ mg/kg body weight}$$

$$20 \text{ mg tadalafil} \div 70 \text{ kg body weight} = 0.29 \text{ mg/kg body weight}$$

170. The approved tadalafil doses would still satisfy the claimed range if the POSA assumed other weights; for example, double or triple body weight.

171. ***Sildenafil.*** Claims 44, 47, 50, 53, and 56 recite a dose range for sildenafil of 0.1 mg to 2 mg per kilogram of patient body weight.

172. The POSA would have known that sildenafil was approved in three oral

dosage forms: 25 mg, 50 mg, and 100 mg tablets. *See* EX1007, 1. Using a patient body weight of 70 kg, any of the commercially available dosages of sildenafil (*e.g.*, Viagra® or Revatio® tablets) of 20 mg, 25 mg, 50 mg, or 100 mg would fall within the scope of claims 44, 47, 50, 53, and 56, as shown by the below calculations:

$$20 \text{ mg sildenafil} \div 70 \text{ kg body weight} = 0.29 \text{ mg/kg body weight}$$

$$25 \text{ mg sildenafil} \div 70 \text{ kg body weight} = 0.36 \text{ mg/kg body weight}$$

$$50 \text{ mg sildenafil} \div 70 \text{ kg body weight} = 0.71 \text{ mg/kg body weight}$$

$$100 \text{ mg sildenafil} \div 70 \text{ kg body weight} = 1.43 \text{ mg/kg body weight}$$

173. The approved sildenafil doses would still satisfy the claimed range if the POSA assumed other weights; for example, double or triple body weight.

174. Thus, the POSA would have immediately understood that Bollis' disclosure of the combination of macitentan and sildenafil or tadalafil would meet the dose limitations of these claims.

175. The POSA would have also understood how to adjust the dosage of a drug such as an endothelin receptor antagonist or a PDE5 inhibitor based on a given patient's needs, medical history, body weight, other drugs the patient may be taking, lifestyle, tolerance, and other factors specific to the patient. For example, when describing the amounts of active ingredients to be administered to a patient, the '847 patent tells the POSA that "the exact administration doses . . . will have to be determined by the treating physician." EX1001, 4:7-9. I agree.

176. Accordingly, Bolli anticipates each of claims 24, 27, 30, 33, 36, 44, 47, 50, 53, and 56.

B. Obviousness in view of Bolli and Keyser.

177. Claims 1-57 are obvious in view of Bolli and Keyser.

178. As I explain above, Bolli teaches macitentan as one of its preferred endothelin receptor antagonist compounds.

179. I understand that WO2006/026395 (Keyser) is the published version of an international patent application titled “Endothelin A Receptor (ETA) Antagonists In Combination With Phosphodiesterase 5 Inhibitors (PDE5) And Uses Thereof.” EX1005, [54]. I also understand that Keyser published on March 9, 2006, and is therefore prior art under pre-AIA 35 U.S.C. §§ 102(a) and (e). *See id.*, [43].

180. 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]. Additionally, Keyser discloses that, while PDE5 inhibitors such as sildenafil are effective treatments, they have several adverse effects and require high doses when administered as a monotherapy. *See, e.g., id.*, [009]. To solve this problem, Keyser teaches a complementary treatment approach by combining a PDE5 inhibitor with an ET_A antagonist to reduce dosage amounts and side effects. *See* EX1005 [067]-[069]. Keyser includes data from a pharmacokinetic drug interaction study showing the

combination of sitaxsentan (an ET_A antagonist) with sildenafil (a PDE5 inhibitor) was well-tolerated. *See id.*, Example 1. Keyser specifically claims and teaches the use of an ET_A antagonist selected from the group consisting of . . . vardenafil, tadalafil, . . . [and] sildenafil[.]” EX1005, 32 (claim 7).

181. Based on Keyser’s disclosure of combinations of an ET_A antagonist and PDE5 inhibitor, as well as Bolli’s disclosure teaching the POSA to combine macitentan with one or more vasodilators (*e.g.*, a PDE5 inhibitor), the POSA would have had reason to combine macitentan with at least one PDE5 inhibitor and would have expected the resulting combination to be a safe and effective treatment for a disease associated with vasoconstriction.

182. The POSA would also have had reason to combine an ET_A antagonist with a PDE5 inhibitor for several reasons.

183. First, Bolli and Keyser each teach the POSA to combine macitentan with a PDE5 inhibitor.

184. Bolli teaches that its compounds, including macitentan, may be used in combination with one or more vasodilators. *Supra* §VII.A. As explained above, the POSA knew vasodilators include tadalafil and sildenafil. *Supra* §VII.A, ¶¶ 92-99; §VII.A.1.a.3, ¶¶ 108-09. For example, Viagra® and Cialis® were widely known and commonly prescribed PDE5 inhibitors available at the time of the priority date of the ’847 patent. Additionally, as I explain above, the POSA knew of the ongoing

efforts by others in the art to devise a treatment for hypertension or PH involving administration of a PDE5 inhibitor such as sildenafil or tadalafil, as well as efforts to devise combination therapies involving administration of sildenafil or tadalafil along with an endothelin receptor antagonist.

185. Keyser expressly teaches combining an ET_A antagonist with a PDE5 inhibitors such as sildenafil, tadalafil, and vardenafil for the advantageous benefit of treating disorders including PAH. *Supra* §VII.B; *see also* EX1005, [57] (teaching “combination therapies comprising an endothelin A receptor (ET_A) antagonist and a phosphodiesterase 5 (PDE5) inhibitor . . . [for] treating various disorders . . . such as pulmonary arterial hypertension (PAH).”); *id.*, [047] (“In another embodiment, the PDE5 inhibitor is tadalafil. In yet another embodiment, the PDE5 inhibitor is sildenafil.”).

186. Second, the POSA would have understood the well-known benefits of combination treatment using drugs having discrete mechanisms of action. *Supra* §V.A. In particular, the POSA would have expected the combination comprising an endothelin antagonist and a PDE5 inhibitor to target two distinct pathways and for this combination to be complementary because while the endothelin receptor antagonist directly blocks the vasoconstrictive effect of ET-1, the PDE5 inhibitor concomitantly enhances the vasodilatory effects of cGMP by preventing degradation of nitric oxide. *Supra* §V.A.

187. Further still, it would have been obvious and a matter of common sense to the POSA to use macitentan in Keyser's combination treatments because, as explained above, the POSA would have understood from Bolli that macitentan is a selective ET_A receptor antagonist. *Supra* §V.D.1. The POSA understands that greater activity in blocking the ET_A receptor with an endothelin receptor antagonist helps prevent this vasoconstriction, thereby improving blood flow and reducing pulmonary pressure. *See supra* §V.A.

188. Hence, the POSA would have had reason to combine macitentan with a PDE5 inhibitor.

189. Moreover, the POSA would have reasonably expected success when combining Bolli's and Keyser's teachings, which expressly recognize the benefits of such a combination. The POSA would have been able to obtain and provide to a patient the administration of the two drugs, as enumerated in the prior art. The POSA would also have reasonably expected that macitentan and a PDE5 inhibitor to be a safe drug combination which is capable of lowering blood pressure based on Bolli and Keyser's general disclosure, as well as Keyser's disclosure of results of a pharmacokinetics study of healthy volunteers who received a combination treatment of sitaxsentan—an ET_A antagonist—and sildenafil. *See* EX1005, [093]-[097].

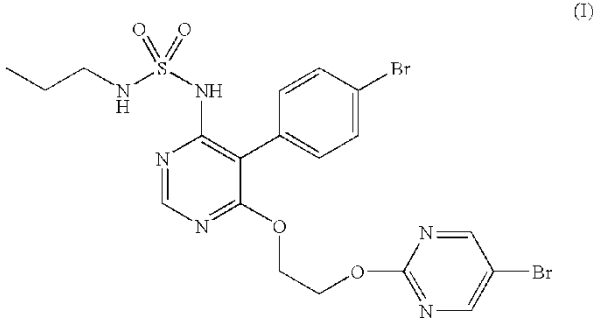
1. Product claims 1-5

190. Bolli and Keyser render the product claims (*i.e.*, claims 1-5) of the '847

patent obvious.

a) Claim 1

191. Independent claim 1 recites:

Claim 1	
[1.Preamble]	1. A product containing
[1.1]	the compound of formula (I) below
	 (I)
[1.2]	in free or pharmaceutically acceptable salt form,
[1.3]	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.

192. As I explain above, Bolli teaches the elements of claim 1. *Supra* §VII.A.1.

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

193. As I explain above, Bolli teaches a product. *Supra* §VII.A.1.

194. Keyser also teaches a product. For example, Keyser claims pharmaceutical compositions comprising an ET_A antagonist, a PDE5 inhibitor and a

pharmaceutical carrier. EX1005, claims 34-43; *see also id.*, [57] (disclosing “combination therapies” and “pharmaceutical compositions”).

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

195. As I explain above, Bolli discloses macitentan in free or pharmaceutically acceptable salt form. *Supra* §VII.A.1. Keyser further teaches that the PDE5 inhibitor and ET_A antagonist 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]

196. Claim 1 further requires that macitentan is provided in combination with at least one compound having PDE5-inhibitory properties, in free or a pharmaceutically acceptable salt form. As I explain above, Bolli teaches this feature of claim 1. *Supra* §VII.A.1.

197. Further, Keyser teaches “combination therapies comprising an endothelin A receptor (ET_A) antagonist and a phosphodiesterase 5 (PDE5) inhibitor, pharmaceutical compositions comprising ET_A antagonist and PDE5 inhibitor and methods of treating various disorders comprising administering an ET_A antagonist and a PDE5 inhibitor.” EX1005, [54], [57]. Keyser also teaches that its “combination therapies and pharmaceutical compositions are useful for the treatment and/or prevention of cardiac disorders such as (PAH).” *Id.* “For each of the recited

embodiments,” Keyser further teaches that useful PDE5 inhibitors include, “*e.g.*, . . . tadalafil (CIALIS) . . . and sildenafil.” *Id.*, [046].

198. Keyser expressly teaches a combination of an ET_A antagonist with a PDE5 inhibitor (*e.g.*, sildenafil or tadalafil). *See* EX1005, [009]. Keyser further teaches that the PDE5 inhibitor can be in free or pharmaceutically acceptable salt form. *Id.*, [073].

199. The POSA had ample reasons to combine macitentan with a PDE5 inhibitor with a reasonable expectation of success. Keyser expressly says to combine ET_A antagonists with PDE5 inhibitors. Keyser explains that to address potential problems associated with PDE5 inhibitor monotherapies, “it would be beneficial to combine a PDE5 inhibitor with an ET_A antagonist to provide complementary treatment and reduce dosage amounts and/or side effects related to treatment with PDE5 inhibitors.” *Id.*, [045]. Keyser also teaches that sildenafil, tadalafil, and vardenafil are all useful PDE5 inhibitors, as well as additional PDE5 inhibitors known and described in the art. *Id.*, [046]; *see also id.*, [029].

200. Bolli and Keyser are also in the same field of art regarding the treatment of vasoconstrictive diseases, including ED, PH, and PAH. They also both teach combination therapies involving ET_A inhibitors and vasodilators (*e.g.*, PDE5 inhibitors). As I explain above, the POSA would have also understood the advantages of treating a disease or condition with two or more active ingredients

targeting different biological pathways, as doing so creates the potential for a more effective therapy than either drug as a monotherapy or even more than the additive effects of the drugs administered separately. *See supra* §V.B; *see e.g.*, EX1009, 3-4 (hypothesizing that a combination therapy of bosentan and sildenafil would be “advantageous in the long run.”). The POSA had reasons to combine Bolli and Keyser to implement the PDE5 inhibitors such as sildenafil or tadalafil from the combination therapies in Keyser into the macitentan-vasodilator combinations therapies in Bolli. *See supra* §VII.A.

201. The POSA would have combined macitentan with a PDE5 inhibitor such as sildenafil or tadalafil with a reasonable expectation of success. Bolli teaches that macitentan (a known ET antagonist) is an effective drug for treating vasoconstrictive diseases. *See supra* §V.D.1.

202. Keyser likewise teaches that ET_A inhibitors and PDE5 inhibitors were effective therapeutic agents. *Id.* 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. *See* EX1005, [093]-[097]. Keyser goes on to teach an efficacy study involving “[m]inimal drug interaction and side effects . . . while maintaining successful therapeutic effect.” *See id.*, [098]-[100]. 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. *Id.*

203. Based on Bolli and Keyser, the POSA would have expected the combination of macitentan (a known ET antagonist) and a PDE5 inhibitor such as tadalafil or sildenafil to be a safe and effective treatment for a disease associated with vasoconstriction.

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

204. Claim 1 of the '847 patent also recites that the claimed combination product is “for therapeutic use, simultaneously, separately over a period of time,” Therefore, Bolli teaches this feature of the '847 patent claims.

205. As I explain above, Bolli discloses that its compounds, including macitentan, “mediate[] vasoconstricting and proliferative responses.” EX1004, 2; *Supra* §VII.A.1.

206. The combination therapies and pharmaceutical compositions comprising ET_A antagonists and PDE5 inhibitors taught by Bolli and Keyser are taught to be “useful for the treatment and/or prevention of cardiac disorders such as [PAH].” EX1005, [57], [002]. Keyser defines the vascular condition treated by its methods 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.” *Id.*, 33 (claim 15); *see also id.*, [030], [031], [069]. The purpose of treatment plainly is for therapeutic use. Keyser also teaches that the ET_A antagonist and PDE5 inhibitor can be provided in a dual dosage form (*i.e.*, simultaneously) or in separate dosage forms substantially concurrently or sequentially. *See id.*, [032]; *see also id.*, 33 (where claim 17 recites a method of treating a vascular condition by administering effective amounts of a) an ET_A antagonist and b) a PDE5 inhibitor “substantially concurrently” and claim 18 recites a method of treating a vascular condition by administering effective amounts of a) an ET_A antagonist and b) a PDE5 inhibitor “sequentially”).

207. Accordingly, Bolli and Keyser render claim 1 of the ’847 patent obvious.

b) Claims 2-4

208. Claims 2-4 recite:

2. The product according to claim 1, wherein the compound having PDE5-inhibitory properties is selected from sildenafil, vardenafil, tadalafil and udenafil.
3. The product according to claim 2, wherein the compound having PDE5-inhibitory properties is tadalafil.
4. The product according to claim 2, wherein the compound having PDE5-inhibitory properties is sildenafil.

209. Dependent claims 2-4 define the PDE5 inhibitor present in the product of claim 1. Claim 2 specifies that “the compound having PDE5-inhibitory properties

is selected from sildenafil, vardenafil, tadalafil and udenafil.” Dependent claim 3 specifies that the PDE5 inhibitor is tadalafil. Dependent claim 4 specifies that it is sildenafil.

210. As I explain above, the POSA would have immediately understood Bolli’s disclosure of vasodilators to be combined with macitentan to include sildenafil or tadalafil. *Supra* §VII.A. Keyser teaches that the PDE5 inhibitor in its combinations with an ET_A antagonist can be sildenafil, tadalafil, or vardenafil, among others. *E.g.*, EX1005, 12 (teaching the use of, “*e.g.*, . . . tadalafil (CIALIS) . . . and sildenafil.”); *see also supra* §V.D.2.

211. Accordingly, Bolli and Keyser render claims 2-4 of the ’847 patent obvious.

c) Claim 5

212. Claim 5 recites:

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.

213. Bolli and Keyser each teach the additional limitations of claim 5 for the reasons I provide above with respect to claim 1. *Supra* §VII.B.1; *see also, e.g.*, EX1005, 33 (claim 15); *see also id.*, [030], [031], [069] (teaching treatment of diseases such as “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.”). Accordingly, claim 5 of the ’847 patent is obvious over Bolli and Keyser.

2. Pharmaceutical composition claims 6-9

a) Claim 6

214. Claim 6 recites:

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.

215. Bolli discloses the use of macitentan and vasodilators as active pharmaceutical ingredients, and using sildenafil or tadalafil (PDE5 inhibitors) as vasodilators would have been immediately apparent to the POSA, and obvious, as I explain above with respect to claim 1. *Supra* §VII.B.1 (addressing, among other things, Bolli’s and Keyser’s disclosures, reasons to combine, and expectation of success). Bolli further discloses that its combinations include at least one excipient. *See* EX1004, 12; *see also id.*, 17-18, claims 12-13, 20.

216. Keyser also teaches pharmaceutical compositions comprising at least one excipient. *See* EX1005, [080] (teaching excipients for solid dosage forms); *see also id.*, [079] (describing excipients for controlled release formulations), [084],

[087]-[089] (describing additional excipient options).

217. Accordingly, Bolli and Keyser render claim 6 of the '847 patent obvious.

b) Claims 7-9

218. Claims 7-9 recite:

7. The pharmaceutical composition according to claim 6, wherein the compound having PDE5-inhibitory properties is selected from sildenafil, vardenafil, tadalafil and udenafil.

8. The pharmaceutical composition according to claim 7, wherein the compound having PDE5-inhibitory properties is tadalafil.

9. The pharmaceutical composition according to claim 7, wherein the compound having PDE5-inhibitory properties is sildenafil.

219. For the reasons I provide above with respect to claim 1, the POSA would have had reason to combine macitentan with tadalafil or sildenafil as the PDE5 inhibitor. *Supra* §VII.B.1; *see also, e.g.*, EX1005, [046] (teaching the use of, “*e.g.*, . . . tadalafil (CIALIS) . . . and sildenafil.”).

220. Accordingly, claims 7-9 of the '847 patent are obvious over the teachings of Bolli and Keyser.

3. Method of treatment claims 10-57

221. Bolli and Keyser also render the method of treatment claims (*i.e.*, claims 10-57) of the '847 patent obvious.

a) Claim 10

222. Claim 10 recites:

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.

223. Claim 10 recites a method for the treatment of hypertension or PH comprising administering to a patient in need thereof an effective amount of a compound of formula (I) as described in claim 1 (*i.e.*, macitentan), in free or pharmaceutically acceptable salt form, in combination with at least one compound having PDE5-inhibitory properties, in free or pharmaceutically acceptable salt form.

224. As I explain above, Bolli discloses a “method for the treatment of hypertension or pulmonary hypertension.” *See, e.g.*, EX1004, 3 (“Endothelin receptor antagonists have demonstrated preclinical and/or clinical efficacy in . . . pulmonary and systemic hypertension . . .”), 12 (“Because of their ability to inhibit the endothelin binding, the described compounds can be used for treatment of diseases, which are associated with an increase in vasoconstriction, proliferation or inflammation due to endothelin. Examples of such diseases are hypertension, pulmonary hypertension”); *see also id.*, claims 12, 14, and 18; *see also supra* §VII.B.1 (addressing, among other things, Bolli’s and Keyser’s disclosures, reasons to combine, and expectation of success).

225. Additionally, also as explained above with respect to claim 1, Keyser teaches that its combination therapies and pharmaceutical compositions comprising ET_A antagonists and PDE5 inhibitors are “useful for the treatment and/or prevention of cardiac disorders such as [PAH].” EX1005, [57], [002]; *see also supra* §VII.B.1.

226. Keyser defines the vascular condition treated by its methods 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.” EX1005, 33 (claim 15); *see also id.*, [030], [031], [069]. The purpose of treatment plainly is for therapeutic use. Keyser also teaches that the ET_A antagonist and PDE5 inhibitor can be provided in a dual dosage form (*i.e.*, simultaneously) or in separate dosage forms substantially concurrently or sequentially. *See* EX1005, [032]; *see also id.*, 33 (where claim 17 recites a method of treating a vascular condition by administering effective amounts of a) an ET_A antagonist and b) a PDE5 inhibitor “substantially concurrently” and claim 18 recites a method of treating a vascular condition by administering effective amounts of a) an ET_A antagonist and b) a PDE5 inhibitor “sequentially”).

227. Accordingly, Bolli and Keyser render claim 10 of the '847 patent obvious.

b) Claims 11-13

228. Claims 11-13 recite:

11. The method according to claim 10, wherein the compound having PDE5-inhibitory properties is selected from sildenafil, vardenafil, tadalafil and udenafil.

12. The method of claim 11, wherein the compound having PDE5-inhibitory properties is tadalafil.

13. The method of claim 11, wherein the compound having PDE5-inhibitory properties is sildenafil.

229. As I explain above with respect to claim 1, Bolli and Keyser teach the features of claims 11-13, including the combination of macitentan with a PDE5 inhibitor, such as tadalafil or sildenafil specifically. *Supra* §VII.B.1; *see also, e.g.*, EX1005, 32-33 (claim 7). Accordingly, claims 11-13 of the '847 patent are obvious over the teachings of Bolli and Keyser.

c) Claims 14-17

230. Claims 14-17 recite:

14. The method of claim 12, wherein the method is for the treatment of pulmonary hypertension.

15. The method of claim 14, wherein the pulmonary hypertension is pulmonary arterial hypertension.

16. The method of claim 13, wherein the method is for the treatment of pulmonary hypertension.

17. The method of claim 16, wherein the pulmonary hypertension is pulmonary arterial hypertension.

231. Claims 12-13 require performing the claimed method with tadalafil or

sildenafil, respectively, and claims 14-17 depend from claims 12 or 13 and additionally require treating PH or PAH. As I explain above, Bolli and Keyser teach products, pharmaceutical compositions, and methods of treating PH or PAH using sildenafil and tadalafil. *Supra* §VII.B; *see also, e.g.*, EX1004, 3 (“Endothelin receptor antagonists have demonstrated preclinical and/or clinical efficacy in various diseases such as cerebral vasospasm following subarachnoid hemorrhage, heart failure, pulmonary and systemic hypertension, neurogenic inflammation, renal failure and myocardial infarction.”); *see also, e.g.*, EX1005, 33 (claim 15, describing treatment of erectile dysfunction, atherosclerosis, renal failure, hypertension, congestive heart failure, diabetic nephropathy, diabetic neuropathy, interstitial lung disease, obstructive sleep dyspnea, obstructive sleep apnea or resistant hypertension).

232. Accordingly, claims 14-17 are obvious over the teachings of Bolli and Keyser.

d) Claims 18-22 and 38-42

233. Claims 18-22 and 38-42 recite:

18. The method of claim 15, wherein the compound of formula (I) and tadalafil are administered simultaneously.

19. The method of claim 15, wherein the compound of formula (I) and tadalafil are administered separately.

20. The method of claim 15, wherein the compound of formula (I) and tadalafil are administered over a period of time.

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.

22. The method of claim 21, wherein the interval does not exceed one day.

38. The method of claim 17, wherein the compound of formula (I) and sildenafil are administered simultaneously.

39. The method of claim 17, wherein the compound of formula (I) and sildenafil are administered separately.

40. The method of claim 17, wherein the compound of formula (I) and sildenafil are administered over a period of time.

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.

42. The method of claim 41, wherein the interval does not exceed one day.

234. As an initial matter, these claims are obvious for the same reasons as they are anticipated by Bolli as described above. *Supra* §VII.A.3, ¶¶ 148-61. They are also obvious based on Bolli and Keyser as described further below.

(1) Claims 18 and 38

235. Claims 18 and 38 specify that macitentan and the PDE5 inhibitor (either tadalafil or sildenafil) are administered simultaneously. As I explain above, Bolli teaches the features of claims 18 and 38. *Supra* §VII.A.3, ¶¶ 150-51.

236. As explained above, the '847 patent defines “simultaneously” to mean that two drugs are to be administered by the same administration route and at the

same time. *See* EX1001, 2:15-19. Bolli discloses that macitentan is suitable for oral administration. *See* EX1004, 12 (“The compounds can be administered orally []. Examples of applications are capsules, tablets, [and] orally administered suspensions or solutions[.]”).

237. Additionally, Keyser teaches that ET_A antagonists and PDE5 inhibitors, *e.g.*, tadalafil, can be provided in a dual dosage form (*i.e.*, simultaneously) or in separate dosage forms “substantially concurrently” or “sequentially.” EX1005, [032]. A dual dosage form would provide both drugs at the same time using the same route of administration (“simultaneously”).

238. I further note that I did not see any assertion in the ’847 patent or its file history asserting that there is anything nonobvious about simultaneous administration.

239. It would therefore have been obvious to the POSA to administer macitentan and the PDE5 inhibitor (tadalafil or sildenafil) simultaneously based on Bolli’s and Keyser’s teachings. Accordingly, Bolli and Keyser render claims 18 and 38 of the ’847 patent obvious.

(2) Claims 19 and 39

240. Claims 19 and 39 of the ’847 patent specify that, in the claimed method, macitentan and the PDE5 inhibitor (either tadalafil or sildenafil) are administered separately.

241. I understand from the '847 patent that “separately” means that the two drugs are to be administered by different routes of administration and at approximately the same time. *See* EX1001, 2:20-24.

242. Separate dosage forms are also disclosed, and it would be obvious to have the patient take both drugs at the same time for, among other reasons, convenience and patient adherence.

243. As I explain above, Bolli teaches the features of claims 19 and 39. *Supra* §VII.A.3. For example, in addition to oral administration, Bolli teaches that macitentan can be administered “rectally, parenterally, e.g. by intravenous, intramuscular, subcutaneous, intrathecal or transdermal administration or sublingually or as ophthalmic preparation or administered as aerosol.” *See* EX1004, 12.

244. Keyser teaches that an ET_A antagonist and a PDE5 inhibitor (*e.g.*, tadalafil or sildenafil) can be provided in a dual dosage form (*i.e.*, simultaneously) or in separate dosage forms “substantially concurrently” or “sequentially.” EX1005, [032]. Keyser explains that “sequentially is meant to include 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.” *Id.*, [072]. Keyser thus teaches that separate dosage forms (*e.g.*, oral dosage forms) of ET_A antagonists and the PDE5 inhibitor (*i.e.*, tadalafil or sildenafil) may be provided to be administered at different times. Additionally, Keyser teaches that either ET_A antagonists and/or the PDE5 inhibitor (tadalafil or sildenafil) may be administered orally or by other routes such as “administration to the respiratory tract as a snuff or an aerosol or solution for a nebulizer, or as a microfine powder for insufflation.” *Id.*, [080]-[084] (describing solid dosage forms for oral use), [085]-[087] (describing controlled release oral dosage forms), [088]-[089] (describing liquids for oral administration), and [090] (describing compositions to be administered to the respiratory tract). Hence, Bolli and Keyser each teach various administration routes for ET_A antagonists (macitentan) and for the PDE5 inhibitor (tadalafil or sildenafil).

245. I further note that I did not see any assertion in the ’847 patent or its file history asserting that there is anything nonobvious about separate administration.

246. It would therefore have been obvious to the POSA to administer the ET_A antagonist (macitentan) and the PDE5 inhibitor (tadalafil or sildenafil) separately based on Bolli’s and Keyser’s teachings. Accordingly, Bolli and Keyser render claims 19 and 39 of the ’847 patent obvious.

(3) Claims 20 and 40

247. Claims 20 and 40 specify that macitentan and the

PDE5 inhibitor (either tadalafil or sildenafil) are administered over a period of time. As I explain above, Bolli teaches the features of claims 20 and 40. *Supra* §VII.A.3.

248. It would also be obvious to administer the drugs over a period of time, especially where the diseases at issue are generally chronic (*e.g.*, PH, PAH). In addition, “over a period of time” in the ’847 patent appears distinguished from “separately” by requiring administration where one drug is finished before the other, and they are not “at approximately the same time.” Thus, morning administration of one drug and evening of the other would also appear to satisfy the claims, and such administration is obvious.

249. Additionally, I understand that claims 20 and 40 encompass treatment of a patient with one of the two claimed drugs (*i.e.*, macitentan or the PDE5 inhibitor) followed by treatment with the other claimed drug including administration such that “the entire administration of one of the active ingredients is completed before the administration of the other or others begins.” EX1001, 2:25-35. Such a treatment method includes treatment where the patient receives only, *e.g.*, macitentan and then at some indeterminate time later—which is unspecified by the claims and can be on the order of days, weeks, months or even years—receives tadalafil or sildenafil. Additionally, Keyser teaches varying the route of administration 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]). In view of 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. Treatment of a patient with one of these drugs after they have already received treatment with the other (including treatment months or even years previously) would have been obvious to the POSA since, as I explain above, macitentan and the PDE5 inhibitor (tadalafil, sildenafil) are both known to be useful in the treatment of vasoconstrictive diseases, including PH and PAH. *See supra* §VII.A. 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.

250. I further note that I did not see any assertion in the '847 patent or its file history asserting that there is anything nonobvious about “over a period of time” administration.

251. Furthermore, the POSA generally knew how to determine a dosing regimen for a given patient. EX1001, 4:7-9 (“the exact administration doses . . . will have to be determined by the treating physician.”). Additionally, Bolli and Keyser both teach various dosage forms and administration routes for ET_A antagonists and PDE5 inhibitors, including oral administration among others. *See* EX1004, 12 (describing administration “orally, rectally, parenterally, e.g. by intravenous, intramuscular, subcutaneous, intrathecal or transdermal administration or sublingually or as ophthalmic preparation or administered as aerosol”); EX1005, [075] (“e.g., tablets, capsules, pills, powders, granulates, suspensions, emulsions, solution or gels”), [005] (the prior art includes “intravenous administration of vasodilators”), [062] (describing ET receptor antagonists that are “Intravenous use only”, illustrating another known optional route of administration).

252. As I explain in greater detail above, the POSA also would have understood that different drugs have different ADME characteristics which must be considered in determining a dosing regimen for a particular patient.

253. It would therefore have been obvious to the POSA to administer macitentan and the PDE5 inhibitor (tadalafil or sildenafil) over a period of time based on Bolli’s and Keyser’s teachings. Accordingly, Bolli and Keyser render claims 20 and 40 of the ’847 patent obvious.

(4) Claims 21-22 and 41-42

254. Claims 21 and 41 specify that, in the methods defined by claims 20 and 40, respectively (*i.e.*, wherein macitentan and tadalafil are administered over a period of time), the interval between the administration of macitentan and the administration of tadalafil does not exceed two days. Claims 22 and 42 specify that this interval between the administration of macitentan and the administration of tadalafil does not exceed one day. As explained above, Bolli teaches the features of claims 21-22 and 41-42. *Supra* §VII.A.3. Additionally, Bolli teaches “[i]n general the dosage [of macitentan] given ***daily*** in oral form should be between about 3 mg and about 3 g,” and “[t]he dosage should be administered preferably in 1 to 3 doses ***per day*** which are of equal weight.” EX1004, 18 (emphases added).

255. Keyser teaches varying the route of administration and the “interval” between drugs. 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 ETA antagonist can be administered “sequentially in either order,” (EX1005, [025]) and that “sequentially is meant to include variations such as every other day treatment.” (EX105, [072]). In view of 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. 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. 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. EX1001, 2:27-35.

256. Keyser also teaches “[t]he exact formulation, route of administration, and dosage is determined by an individual physician in view of the patient’s condition [and that] [d]osage amount and interval can be adjusted individually to provide levels of the active agents that are sufficient to maintain therapeutic or prophylactic effects.” EX1005, [071]. The POSA also would have known that “[t]he maximum recommended dosing frequency [for tadalafil] is once per day in most patients.” EX1008, 19. Daily administration of one dose of tadalafil and one, two, or three daily doses of macitentan would meet the limitations of claims 21-22.

257. I further note that I did not see any assertion in the ’847 patent or its file history asserting that there is anything nonobvious about the timing limitations of claims 21 and 41 or 22 and 42.

258. Accordingly, claims 21-22 and 41-42 of the '847 patent are obvious over the teachings of Bolli and Keyser.

e) Claims 23-37 and 43-57

(1) Macitentan dosage claims 23, 25, 26, 28, 29, 31, 32, 34, 35, 37, 43, 45, 46, 48, 49, 51, 52, 54, 55, and 57

259. Claims 23, 25, 26, 28, 29, 31, 32, 34, 35, 37, 43, 45, 46, 48, 49, 51, 52, 54, 55, and 57 recite:

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

260. As I explain above, Bolli teaches these dosages of macitentan. *Supra* §VII.A.3. The doses are also obvious in view of Bolli, especially using the known 70 kg body weight that the POSA would have assumed for adults. Bolli teaches administration of macitentan in a range of “dosages of 0.1-50 mg / kg body weight per day,” which substantially overlaps the claimed range of 0.05 mg to 2 mg per kilogram of patient body weight and encompasses the entire claimed range of 0.1 mg to 1 mg per kilogram of patient body weight. *See* EX1004, 12. Bolli goes on to also teach the overlapping macitentan dosage ranges of “between about 3 mg and about 3 g, preferably between about 10 mg and about 1 g, especially preferred between 5 mg and 300 mg, per adult with a body weight of about 70 kg.” *Id.*, 18. The POSA would have understood, by simply dividing these doses by the 70 kg mass (“body weight”) that 3 mg for a 70 kg adult is about 0.04 mg/kg body weight and that 3 g is 3,000 mg, which is about 43 mg/kg body weight. Likewise, 10 mg to 1 g (1,000 mg) is a range of 0.14-14 mg/kg body weight, and 5-300 mg is a range of 0.07-4.3 mg/kg body weight. Bolli therefore teaches the claimed macitentan dose ranges.

261. Additionally, Keyser teaches “[d]aily amounts for ET_A antagonists will be in the range of 5 mg to 125 mg.” EX1005, [074]. Using the 70 kg body weight from Bolli, these doses would be $5/70 = 0.07$ mg/kg and $125/70 = 1.8$ mg/kg body weight. This range (0.07 mg/kg to 1.8 mg/kg) encompasses the entire claimed range of 0.1-1 mg/kg. Thus, the POSA would have understood Keyser’s disclosed range encompasses or overlaps the ranges of these claims.

262. Therefore, Bolli and Keyser render claims 23, 25, 26, 28, 29, 31, 32, 34, 35, 37, 43, 45, 46, 48, 49, 51, 52, 54, 55, and 57 obvious.

(2) PDE5 inhibitor dosage claims 24, 27, 30, 33, 36, 44, 47, 50, 53, and 56

263. Claims 24, 27, 30, 33, 36, 44, 47, 50, 53, and 56 recite:

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

264. Keyser teaches “[d]aily amounts for PDE5 inhibitors will be in the range of 50 mg to 250 mg.” EX1005, [074]. Using the 70 kg body weight from Bolli, these doses would be $50/70 = 0.7$ mg/kg and $250/70 = 3.6$ mg/kg body weight. This range includes the claimed range of 0.1-2 mg/kg. Thus, the daily amounts taught by Keyser correspond to a range of mg/kg body weight dosages that overlap and include the claimed ranges of 0.01-1 mg tadalafil per kg body weight and 0.1-2 mg sildenafil per kg body weight and make those ranges obvious.

265. Accordingly, Bolli and Keyser teach the claimed tadalafil and sildenafil dosages and therefore render claims 24, 27, 30, 33, 36, 44, 47, 50, 53, and of the ’847 patent obvious.

C. Hoeper, Morice, and Bolli render claims 1-57 obvious.

266. Claims 1-57 are obvious in view of Hoeper, Morice, and Bolli.

267. As explained above, there were ongoing efforts by physicians and researchers to investigate combination therapies for cardiovascular diseases such as hypertension and PH leading up to the priority date of the ’847 patent. *See supra* §VII.A. Among these efforts were studies directed to the combination of drug classes

described by Bolli and claimed by the '847 patent.

268. One study directed to a combination of an endothelin receptor antagonist and a PDE5 inhibitor by Hoeper *et al.* was published in the European Respiratory Journal on December 1, 2004, and titled “Combination therapy with bosentan and sildenafil in idiopathic pulmonary arterial hypertension.” *See* EX1009.

269. Hoeper investigated a combination therapy comprising bosentan and sildenafil for treatment of IPAH. *See id.*, 2-4. As described in the paper, Hoeper found that administering sildenafil to patients already receiving bosentan improved their results. *Id.*, 1. Hoeper provides several rationales for choosing the specific non-selective endothelin receptor antagonist (bosentan) and PDE5 inhibitors (sildenafil), including the fact that “both substances are orally available, act via different mechanisms and are usually well tolerated.” *Id.* Indeed, the POSA would have readily considered approved products in their approved dosage forms.

270. Hoeper’s combination therapy of bosentan and sildenafil resulted in significant improvements in patients’ exercise capacities (as indicated by their six-minute walk distances), hemodynamic parameters such as pulmonary vascular resistance and mean pulmonary arterial pressure, and overall clinical health. *Id.*, 2-3. Hoeper’s combination treatment was well tolerated by all patients with no major side effects. *Id.*, 3.

271. In addition to the combination of an endothelin receptor antagonist

(bosentan) and a PDE5 inhibitor (sildenafil), Hoeper teaches an administration method in which sildenafil dosages were adjusted. *Id.*, 2. Consistent with Hoeper, the POSA generally knew how to adjust the dosage of a drug such as an endothelin receptor antagonist or a PDE5 inhibitor based on a given patient's needs, medical history, body weight, other drugs the patient may be taking, lifestyle, tolerance, and other factors specific to the patient.

272. In response to Hoeper, Morice *et al.* submitted a comment to the editors of the European Respiratory Journal, which was published on July 1, 2005. EX1010, 1. Morice describes an alternative combination of bosentan (like in Hoeper) and tadalafil (Hoeper described use of sildenafil), specifically involving 20 mg of tadalafil administered once daily. *See id.* Thus, a POSA would have considered the teachings of Hoeper and Morice together.

273. A POSA would also have considered the teachings of Hoeper and Morice together with the teachings of Bolli. As I explain above, Bolli discloses macitentan as a preferred endothelin receptor antagonist. *See supra* §VII.A.1; *see also, e.g.*, EX1004, 25, 29 (describing macitentan shown on page 28 of Bolli as a member of “[a]nother group of preferred compounds [] depicted below.”). In view of Hoeper's teachings and the POSA's general knowledge regarding the usefulness of PDE5 inhibitors as vasodilators, the POSA would have had reason to combine a PDE5 inhibitor such as sildenafil or tadalafil as taught in Hoeper and Morice with

macitentan as taught in Bolli. Additionally, the POSA would have found the claimed dosage limitation obvious based on the POSA's background knowledge of approved drug labels and common practices for dosing those drugs for individual patients.

274. There are several reasons the POSA would have combined these references with a reasonable expectation of success. Bolli expressly teaches combination therapies with preferred compounds, including macitentan. *See* EX1004, 25, 29 (describing macitentan shown on page 28 of Bolli as a member of “[a]nother group of preferred compounds [] depicted below.”). Hoeper discloses combination therapy of bosentan and sildenafil, with promising results. Morice discloses that bosentan and tadalafil are also an effective combination. Thus, the POSA had reason to use the preferred macitentan compound of Bolli with the PDE5 inhibitors in Hoeper and Morice (sildenafil and tadalafil). Further, even if the POSA did not have reason to use macitentan with sildenafil and tadalafil, those combinations would be obvious to try as Bolli preferred macitentan and sildenafil and tadalafil were effective active ingredients in two blockbuster drugs, Viagra® and Cialis®.

275. Further still, it would have been obvious and a matter of common sense to the POSA to use macitentan instead of bosentan in Hoeper or Morice's combination treatments because, as explained above, the POSA would have understood from Bolli that macitentan, like bosentan, is an ET_A receptor antagonist,

and that macitentan showed selectivity for the ET_A receptor. *Supra* §V.D.1. The POSA would have understood that greater activity in blocking the ET_A receptor with an endothelin receptor antagonist helps prevent this vasoconstriction, thereby improving blood flow and reducing pulmonary pressure. *See supra* §V.A.

276. The POSA would also have reasonably expected success based on the disclosed benefits of each compound and the benefits they teach for combination therapies of compounds with different mechanisms of action, and I am unaware of any argument in the patent or its file history asserting that the POSA would not have expected to be able to administer the combinations or that they would be unsafe. Thus, each of claims 1-57 of the '847 patent is obvious based on the teachings of Hoeper, Morice, and Bolli.

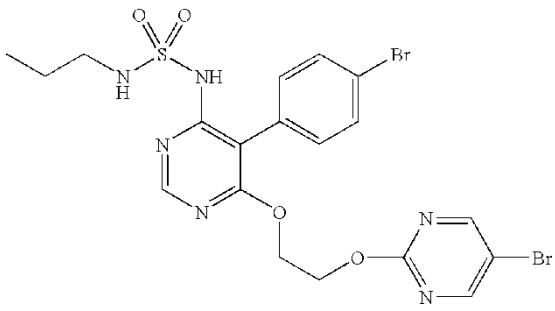
1. Product claims 1-5

277. Hoeper, Morice, and Bolli render the product claims (*i.e.*, claims 1-5) of the '847 patent obvious.

a) Claim 1

278. Independent claim 1 recites:

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.

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

279. As I explain above, Bolli teaches products, including pharmaceutical compositions, which contain macitentan and at least one vasodilator such as a PDE5 inhibitor, for the treatment of a disease involving vasoconstriction (*e.g.*, hypertension, PH, PAH, ED, and the like). *Supra* §VII.A.1.

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

281. Additionally, Morice reported a combination treatment of bosentan and tadalafil. EX1010, 1. Morice’s treatment involved administration of bosentan and 20 mg of tadalafil once daily. *Id.*

(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]

282. Bolli teaches the compound of formula (I) recited in claim 1 of the '847 patent—*i.e.*, macitentan—for the reasons I discuss above. *Supra* §VII.A.1.

283. Hoeper teaches the use of another endothelin receptor antagonist, bosentan, in combination with sildenafil. *See, e.g.*, EX1009, 1 (describing combining bosentan and sildenafil).

284. The POSA would have had reason to substitute the macitentan from Bolli for the bosentan in the Hoeper's combination based on their knowledge of bosentan's properties in the context of the claimed combination products. The POSA would have understood bosentan is potent for both ET_A and ET_B and thus implicates multiple biological pathways, including cGMP production by ET_B. The POSA would have understood an ET antagonist which is more potent for ET_A than ET_B—like macitentan—would be preferable because such an ET antagonist would inhibit vasoconstriction more than it would inhibit vasodilation.

285. As explained above, Bolli teaches ET_A and ET_B IC₅₀ values for exemplary endothelin receptor antagonists, including homologs of macitentan. *See* EX1004, 5-9 (Table 1); *supra* §V.D.1. Knowledgeable of the mechanisms of action of ET_A antagonists, ET_B antagonists, and PDE5 inhibitors, the POSA would have had reason to replace bosentan in Hoeper's combination with an endothelin receptor

antagonist taught by Bolli to be selective for ET_A over ET_B because the POSA knew bosentan to have only minimal selectivity for ET_A over ET_B. *See* EX1027, 3; *see also supra* §VII.C.1. Macitentan, on the other hand, was understood by the POSA to be highly selective for ET_A over ET_B as I explain in detail above in Section V.D.1 and in further detail below.

286. Also, as explained above, Bolli's Example 104 is substantially more potent for ET_A than ET_B, having an ET_A IC₅₀ of 0.88 nM and an ET_B IC₅₀ of 601 nM. EX1004, 6 (Table 1); *supra* §V.D.1. The POSA would have expected Example 104 and macitentan—which are consecutive members of a homologous series differing only by a single carbon in a straight-chain alkyl group—to have the same or substantially similar properties (*e.g.*, IC₅₀ values). Indeed, Bolli describes Example 104 and its homologs, including macitentan, as preferred compounds. *See* EX1004, 25-29. The POSA would thus have had reason to combine macitentan with sildenafil in place of bosentan in Hoeper's combination.

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

287. Element [1.3] is also obvious based on the teachings of Hoeper, Morice, and Bolli because each of these prior art references teaches treatment of a disease wherein vasoconstriction is involved by administering a combination of an endothelin receptor antagonist and a PDE5 inhibitor to treat, *e.g.*, PH, PAH, IPAH,

and other diseases involving vasoconstriction. *See* EX1004, 12 (describing use of the disclosed compounds, including macitentan, “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”); *see* EX1009, 1, (describing combining bosentan and sildenafil to treat IPAH); *see also, e.g.*, EX1010, 1 (describing combining bosentan and tadalafil to treat PAH).

288. Hoeper, Morice, and Bolli also teach administration of the two compounds “simultaneously, separately[,] or over a period of time.” *Supra* §VI.B.1.b. The ’847 patent defines “simultaneously” and “simultaneous,” “separately” or “separate,” and “over a period of time” as follows:

“Simultaneously” or “simultaneous”, when referring to a therapeutic use, means in the present application that the therapeutic use concerned consists in the administration of two or more active ingredients by the same route and at the same time.

“Separately” or “separate”, when referring to a therapeutic use, means in the present application that the therapeutic use concerned consists in the administration of two or more active ingredients at approximately the same time by at least two different routes.

By therapeutic administration “over a period of time” is meant in the present application the administration of two or more ingredients at different times, and in particular an administration method according to which the entire administration of one of the active ingredients is completed before the administration of the other or others begins. In this way it is possible to administer one of the active ingredients for several months before administering the other active ingredient or ingredients. In this case, no simultaneous administration occurs.

EX1001, 2:14-38.

289. Additionally, as I explain in greater detail below with respect to claims 18-20 and 38-40 of the '847 patent, Hoeper, Morice, and Bolli teach various routes of administration of macitentan, and the POSA knew sildenafil (Viagra®) and tadalafil (Cialis®) to be commercially available in their FDA-approved oral dosage forms. *See infra*, §VII.A.3.d. Hence, co-administration of an oral PDE5 inhibitor (*e.g.*, sildenafil or tadalafil) and macitentan by any of the routes disclosed by Bolli—rectally, parenterally (*e.g.*, intravenously, intramuscularly, subcutaneously, intrathecally, transdermally) sublingually, or via ophthalmic or aerosol preparations—would meet the claimed simultaneous or separate administration limitations of the '847 patent claims in accordance with how the patent specification defines those terms. *See* EX1004, 12.

290. Additionally, as acknowledged by Patent Owner, the POSA generally would have known how to determine a dosing regimen for a given patient. EX1001, 4:7-9 (“[T]he exact administration doses . . . will have to be determined by the treating physician.”). Based on the teachings of Hoeper, Morice, and Bolli each teaching oral administration (*i.e.*, administration by the same route), the POSA would have found it obvious to administer both macitentan and the PDE5 inhibitor (tadalafil or sildenafil) together at the same time for, *e.g.*, patient compliance and convenience.

291. Hoeper, Morice, and Bolli also teach administration of macitentan and a PDE5 inhibitor “over a period of time” as that term is defined in the ’847 patent. The POSA would have been led by these references to administer macitentan and a PDE5 inhibitor at different times because, for example, Hoeper teaches daily administration of three or four doses of sildenafil and two doses of bosentan, and Morice teaches daily administration of one dose of tadalafil with the bosentan doses taught by Hoeper, meaning at least one dose of Hoeper’s sildenafil is administered without an endothelin receptor antagonist (bosentan) and at least one dose of Morice’s bosentan is administered without tadalafil. *See* EX1009, 2; *see* EX1010, 1; *see also infra* §VII.C.3.d.

292. Moreover, the broad definition for administration “over a period of time” provided by the ’847 patent includes administration of a first active ingredient “for several months before administering the other active ingredient or ingredients” such that “no simultaneous administration occurs.” *See* EX1001, 2:25-35. The ’847 patent thus appears to try to encompass administration of macitentan and a PDE5 inhibitor according to all conceivable timings and administration routes, each of which is taught by Bolli. Indeed, Actelion acknowledges in the ’847 patent itself that each claimed administration timing was fully within the POSA’s knowledge and capabilities. *See* EX1001, 4:7-9 (“the exact administration doses . . . will have to be determined by the treating physician.”).

293. The POSA would thus have understood that the combination taught by Hoeper, Morice, and Bolli would include administration of the two drugs “simultaneously,” “separately,” and “over a period of time.”

294. Additionally, Hoeper teaches treatment of patients with a combination of bosentan and sildenafil from January 2002 to December 2003. EX1009, 1. Hoeper’s treatment schedule involved administering sildenafil to patients already taking bosentan. *See id.* As discussed above, Morice teaches a combination treatment involving simultaneous administration of bosentan and tadalafil. EX1010, 1. Bolli taught the treatment of diseases involving vasoconstriction, including PH. Hoeper’s patients had IPAH and Morice’s had PAH. Both IPAH and PAH are diseases wherein vasoconstriction is involved. Thus, the combination of these references makes this limitation obvious.

295. Accordingly, the teachings of Hoeper, Morice, and Bolli render claim 1 of the ’847 patent obvious.

b) Claims 2-4

296. Claims 2-4 recite:

2. The product according to claim 1, wherein the compound having PDE5-inhibitory properties is selected from sildenafil, vardenafil, tadalafil and udenafil.
3. The product according to claim 2, wherein the compound having PDE5-inhibitory properties is tadalafil.
4. The product according to claim 2, wherein the compound having PDE5-inhibitory properties is sildenafil.

297. Additionally, as I explain above, Hoeper, Morice, and Bolli teach that the PDE5 inhibitor in its combinations with an ET_A antagonist can be sildenafil, tadalafil, or vardenafil, among others. *Supra* §VII.C; *see, e.g.*, EX1009, 1 (describing combining bosentan and sildenafil to treat IPAH); *see, e.g.*, EX1010, 1 (describing combining bosentan and tadalafil to treat PAH).

298. Accordingly, it is my opinion claims 2-4 of the '847 patent are obvious over the teachings of Hoeper, Morice and Bolli.

c) Claim 5

299. Claim 5 recites:

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.

300. Hoeper, Morice, and Bolli teach the additional limitations of claim 5 for the reasons I provide above with respect to claim 1, limitation 1.4. *Supra* §VII.C.1.a.3; *see, e.g.*, EX1004, 12 (“[T]he described compounds can be used 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”); *see, e.g.*, EX1009, 1 (describing combining bosentan and sildenafil to treat IPAH); *see, e.g.*, EX1010, 1 (describing combining bosentan and tadalafil to treat PAH). Accordingly, claim 5 of the '847 patent is obvious over Hoeper, Morice, and Bolli.

2. Pharmaceutical composition claims 6-9

a) Claim 6

301. Claim 6 recites:

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.

302. As I explain above, Hoeper, Morice, and Bolli teach the product of claim 1. *Supra* §VII.C.1. They teach a pharmaceutical composition for the same reasons.

303. Bolli discloses the use of macitentan and vasodilators as active pharmaceutical ingredients, and using sildenafil or tadalafil (PDE5 inhibitors) as vasodilators would have been immediately apparent to the POSA, as I explain above with respect to claim 1. *Supra* §VII.A.1.

304. Bolli further discloses that its combinations include “at least one excipient.” *See* EX1004, 12; *see also id.*, 17-18, claims 12-13, 20.

305. Additionally, the POSA would have understood from Hoeper and Morice that administration of sildenafil or tadalafil in the commercially available dosage forms of Viagra® and Cialis® contain excipients. *See* EX1009; EX1010; EX1007, 1; EX1008, 2; *supra* §VII.C.1.

306. Accordingly, claim 6 of the '847 patent is obvious over Hoeper, Morice, and Bolli.

b) Claims 7-9

307. Claims 7-9 recite:

7. The pharmaceutical composition according to claim 6, wherein the compound having PDE5-inhibitory properties is selected from sildenafil, vardenafil, tadalafil and udenafil.

8. The pharmaceutical composition according to claim 7, wherein the compound having PDE5-inhibitory properties is tadalafil.

9. The pharmaceutical composition according to claim 7, wherein the compound having PDE5-inhibitory properties is sildenafil.

308. For the reasons I provide above with respect to claim 1, the POSA would have had reason to combine macitentan with tadalafil or sildenafil as the PDE5 inhibitor. *Supra* §VII.C.1; *see also, e.g.*, EX1009, 1 (describing combining bosentan and sildenafil to treat IPAH); *see also, e.g.*, EX1010, 1 (describing combining bosentan and tadalafil to treat PAH).

309. Accordingly, claims 7-9 of the '847 patent are obvious over the teachings of Hoeper, Morice, and Bolli.

3. Method of treatment claims 10-57

a) Claim 10

310. Claim 10 recites:

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.

311. Claim 10 defines a method for the treatment of hypertension or PH comprising administering to a patient in need thereof an effective amount of a compound of formula (I) as described in claim 1 (*i.e.*, macitentan), in free or pharmaceutically acceptable salt form, in combination with at least one compound having PDE5-inhibitory properties, in free or pharmaceutically acceptable salt form.

312. As I explain above, Hoeper, Morice, and Bolli teach methods of treating hypertension or PH involving administration of combinations of an endothelin receptor antagonist and a PDE5 inhibitor, including a combination of macitentan and sildenafil or tadalafil. *Supra* §V.D; *see also, e.g.*, EX1004, 12 (“[T]he described compounds can be used 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”); *see also, e.g.*, EX1009, 1 (describing combining bosentan and sildenafil to treat IPAH); *see also, e.g.*, EX1010 (describing combining bosentan and tadalafil to treat PAH).

313. Accordingly, claim 10 of the '847 patent is obvious over Hoeper, Morice, and Bolli.

b) Claims 11-13

314. Claims 11-13 recite:

11. The method according to claim 10, wherein the compound having PDE5-inhibitory properties is selected from sildenafil, vardenafil, tadalafil and udenafil.

12. The method of claim 11, wherein the compound having PDE5-inhibitory properties is tadalafil.

13. The method of claim 11, wherein the compound having PDE5 inhibitory properties is sildenafil.

315. As I explain above with respect to claim 1, Hoeper, Morice, and Bolli teach the features of claims 11-13. *Supra* §VII.C.1; *see also, e.g.*, EX1009, 1 (describing combining bosentan and sildenafil to treat IPAH); *see also, e.g.*, EX1010 (describing combining bosentan and tadalafil to treat PAH).

316. Accordingly, claims 11-13 of the '847 patent are obvious over the teachings of Hoeper, Morice, and Bolli.

c) Claims 14-17

317. Claims 14-17 recite:

14. The method of claim 12, wherein the method is for the treatment of pulmonary hypertension.

15. The method of claim 14, wherein the pulmonary hypertension is pulmonary arterial hypertension.

16. The method of claim 13, wherein the method is for the treatment of pulmonary hypertension.

17. The method of claim 16, wherein the pulmonary hypertension is pulmonary arterial hypertension.

318. **Claims 14-15.** Claim 14 depends from claim 12 (requiring tadalafil) and specifies that the method is for the treatment of PH. Claim 15 depends from claim 14 and further specifies that the PH to be treated is PAH. As I explain above, Hoeper, Morice, and Bolli teach products, pharmaceutical compositions, and methods of treating PH or PAH. *Supra* §VII.C; *see also, e.g.*, EX1004, 12 (“[T]he described compounds can be used 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”); *see, e.g.*, EX1010 (describing combining bosentan and tadalafil to treat PAH).

319. **Claims 16-17.** Dependent claim 16 depends from claim 13 (requiring sildenafil) and specifies that the method is for the treatment of PH. Dependent claim 17 depends from claim 16 and further specifies that the PH to be treated is PAH. As I explain above, Hoeper, Morice, and Bolli teach products, pharmaceutical compositions, and methods of treating PH or PAH involving administration of a combination of macitentan and a tadalafil or sildenafil. *Supra* §VII.C; *see also, e.g.*, EX1004, 12 (“[T]he described compounds can be used 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”); *see, e.g.*, EX1009, 1 (describing

combining bosentan and sildenafil to treat IPAH).

320. Accordingly, claims 14-17 are obvious over the teachings of Hoeper, Morice, and Bolli. *Supra* §VII.C.3.

d) Claims 18-22 and 38-42

321. Claims 18-22 and 38-42 recite:

18. The method of claim 15, wherein the compound of formula (I) and tadalafil are administered simultaneously.

19. The method of claim 15, wherein the compound of formula (I) and tadalafil are administered separately.

20. The method of claim 15, wherein the compound of formula (I) and tadalafil are administered over a period of time.

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.

22. The method of claim 21, wherein the interval does not exceed one day.

38. The method of claim 17, wherein the compound of formula (I) and sildenafil are administered simultaneously.

39. The method of claim 17, wherein the compound of formula (I) and sildenafil are administered separately.

40. The method of claim 17, wherein the compound of formula (I) and sildenafil are administered over a period of time.

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.

42. The method of claim 41, wherein the interval does not exceed one day.

322. As an initial matter, these claims are obvious for the same reasons as

they are anticipated by Bolli or rendered obvious by Bolli in view of Keyser as described above. *Supra* §VII.A.3. They are also obvious over Hoeper in view of Morice and Bolli as described further below.

(1) Claims 18 and 38

323. Claims 18 and 38 specify that macitentan and the PDE5 inhibitor (either tadalafil or sildenafil) are administered simultaneously. As I explain above, Bolli teaches the features of claims 18 and 38. *Supra* §VII.A.3.

324. I understand from the '847 patent that “simultaneously” means that two drugs are to be administered by the same administration route and at the same time. *See* EX1001, 2:15-19. Bolli discloses that macitentan is suitable for oral administration. *See* EX1004, 12 (“The compounds can be administered orally []. Examples of applications are capsules, tablets, [and] orally administered suspensions or solutions[.]”). Hoeper and Morice also both teach oral administration of sildenafil and tadalafil, respectively. EX1009; EX1010.

325. As acknowledged by Patent Owner, the POSA generally knew how to determine a dosing regimen for a given patient. EX1001, 4:7-9 (“[T]he exact administration doses . . . will have to be determined by the treating physician.”). Based on the teachings of Hoeper, Morice, and Bolli each teaching oral administration (*i.e.*, administration by the same route), the POSA would have found

it obvious to administer both macitentan and the PDE5 inhibitor (tadalafil or sildenafil) together at the same time for, *e.g.*, patient compliance and convenience.

326. I further note that I did not see any assertion in the '847 patent or its file history asserting that there is anything nonobvious about simultaneous administration.

327. It would therefore have been obvious to the POSA to administer macitentan and the PDE5 inhibitor (tadalafil or sildenafil) simultaneously based on Hoeper, Morice, and Bolli's teachings. Accordingly, the teachings of Hoeper, Morice, and Bolli render claims 18 and 38 of the '847 patent obvious.

(2) Claims 19 and 39

328. Claims 19 and 39 of the '847 patent specify that, in the claimed method, macitentan and the PDE5 inhibitor (either tadalafil or sildenafil) are administered separately.

329. I understand from the '847 patent that "separately" means that the two drugs are to be administered by different routes of administration and at approximately the same time. *See* EX1001, 2:20-24.

330. Separate dosage forms are also disclosed, and it would be obvious to have the patient take both drugs at the same time for, among other reasons, convenience and patient adherence.

331. As I explain above, Hoeper teaches oral administration of bosentan with

sildenafil and Morice teaches oral administration of bosentan with tadalafil. *Supra* §VII.C; *see also* EX1009; EX1010. As I also explain above, Bolli teaches that, in addition to oral administration, macitentan can be administered “rectally, parenterally, e.g. by intravenous, intramuscular, subcutaneous, intrathecal or transdermal administration or sublingually or as ophthalmic preparation or administered as aerosol.” *See* EX1004, 12. Accordingly, Hoeper, Morice, and Bolli together teach methods of treating patients using different administration routes for macitentan and the PDE5 inhibitor (tadalafil or sildenafil). The POSA would have found it obvious to administer these drugs at the same time or approximately the same time for, among other reasons, convenience and patient adherence.

332. I further note that I did not see any assertion in the ’847 patent or its file history asserting that there is anything nonobvious about separate administration.

333. It would therefore have been obvious to the POSA to administer macitentan and the PDE5 inhibitor (tadalafil or sildenafil) separately based on Hoeper, Morice, and Bolli’s teachings. Accordingly, the teachings of Hoeper, Morice, and Bolli render claims 19 and 39 of the ’847 patent obvious.

(3) Claims 20 and 40

334. Claims 20 and 40 specify that macitentan and the PDE5 inhibitor (either tadalafil or sildenafil) are administered over a period of time. As I explain above, Bolli teaches the features of claims 20 and 40. *Supra* §VII.A.3.

335. It would also be obvious to administer the drugs over a period of time, especially where the diseases at issue are generally chronic (*e.g.*, PH, PAH). In addition, “over a period of time” in the ’847 patent appears distinguished from “separately” by requiring administration where one drug is finished before the other, and they are not “at approximately the same time.” Thus, morning administration of one drug and evening of the other would also appear to satisfy the claims, and such administration is obvious.

336. Additionally, I understand that claims 20 and 40 encompass treatment of a patient with one of the two claimed drugs (*i.e.*, macitentan or the PDE5 inhibitor) followed by treatment with the other claimed drug such that “the entire administration of one of the active ingredients is completed before the administration of the other or others begins.” EX1001, 2:25-35. Such a treatment method includes treatment where the patient receives only, *e.g.*, macitentan and then at some indeterminate time later—which is unspecified by the claims and can be on the order of days, weeks, months or even years—receives tadalafil or sildenafil. Treatment of a patient with one of these drugs after they have already received treatment with the other (including treatment months or even years previously) would have been obvious to the POSA since, as I explain above, macitentan and the PDE5 inhibitor (tadalafil, sildenafil) are both known to be useful in the treatment of vasoconstrictive diseases, including PH and PAH. *See supra* §VII.A. 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.

337. Additionally, Hoeper teaches treatment involving administration of an endothelin receptor antagonist (bosentan) twice daily and administration of sildenafil three or four times a day. EX1009, 2. Since Hoeper's treatment method involves an unequal number of bosentan and sildenafil doses, Hoeper teaches administration of at least one dose of sildenafil "over a period of time" relative to a previous dose of bosentan. *See* EX1001, 2:25-35 (defining "over a period of time" to mean "administration of two or more ingredients at different times").

338. I further note that I did not see any assertion in the '847 patent or its file history asserting that there is anything nonobvious about "over a period of time" administration.

339. It would therefore have been obvious to the POSA to administer macitentan and the PDE5 inhibitor (tadalafil or sildenafil) over a period of time based on Hoeper, Morice, and Bolli's teachings. Accordingly, the teachings of Hoeper, Morice, and Bolli render claims 20 and 40 of the '847 patent obvious.

(4) Claims 21-22 and 41-42

340. Claims 21 and 41 specify that, in the methods defined by claims 20 and 40, respectively (*i.e.*, wherein macitentan and tadalafil are administered over a period of time), the interval between the administration of macitentan and the

administration of tadalafil does not exceed two days. Claims 22 and 42 specify that this interval between the administration of macitentan and the administration of tadalafil does not exceed one day. As explained above, Bolli teaches the features of claims 21-22 and 41-42. *Supra* §VII.A.3, ¶¶ 161-63.

341. Additionally, Bolli teaches “[i]n general the dosage [of macitentan] given ***daily*** in oral form should be between about 3 mg and about 3 g,” and “[t]he dosage should be administered preferably in 1 to 3 doses ***per day*** which are of equal weight.” EX1004, 18 (emphases added).

342. Additionally, Hoeper teaches treatment involving administration of an endothelin receptor antagonist (bosentan) twice daily and administration of sildenafil three or four times a day. EX1009, 2. Hoeper teaches administration of at least one dose of sildenafil “over a period of time” relative to a previous dose of bosentan (*i.e.*, at least one dose of sildenafil without a dose of bosentan). *See* EX1001, 2:25-35 (defining “over a period of time” to mean “administration of two or more ingredients at different times”). The interval between administration of a daily dose of sildenafil by itself and a prior daily dose of bosentan is thus less than one day. Hoeper also discloses that bosentan was administered as a “first-line therapy” before starting sildenafil. EX1009, 1-2.

343. With respect to tadalafil, 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 endothelin receptor antagonist (bosentan) thus involves administration over a period of time since at least one of the bosentan doses is administered without tadalafil. 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.* Thus, the three drugs were taken “over a period of time.”

344. In view of Hoeper, Morice, and Bolli’s disclosures, the POSA would have therefore had reason to administer macitentan and a PDE5 inhibitor (tadalafil or sildenafil) over a period of time wherein the interval between them does not exceed one (or two) days.

345. I further note that I did not see any assertion in the ’847 patent or its file history asserting that there is anything nonobvious about the timing limitations of claims 21 and 41 or 22 and 42.

346. Accordingly, claims 21-22 and 41-42 of the ’847 patent are obvious over the teachings of Hoeper, Morice, and Bolli.

e) Claims 23-37 and 43-57

(1) Macitentan dosage claims 23, 25, 26, 28, 29, 31, 32, 34, 35, 37, 43, 45, 46, 48, 49, 51, 52, 54, 55, and 57

347. Claims 23, 25, 26, 28, 29, 31, 32, 34, 35, 37, 43, 45, 46, 48, 49, 51, 52, 54, 55, and 57 recite:

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

348. As I explain above, Bolli teaches these dosages of macitentan. *Supra* §VII.A.3. Bolli teaches administration of macitentan in a range of “dosages of 0.1-50 mg / kg body weight per day,” which substantially overlaps the claimed range of

0.05 mg to 2 mg per kilogram of patient body weight and encompasses the entire claimed range of 0.1 mg to 1 mg per kilogram of patient body weight. *See* EX1004, 12. Bolli goes on to also teach the overlapping macitentan dosage ranges of “between about 3 mg and about 3 g, preferably between about 10 mg and about 1 g, especially preferred between 5 mg and 300 mg, per adult with a body weight of about 70 kg.” *Id.*, 18. The POSA would have understood, by simply dividing these doses by the 70 kg mass (“body weight”) that 3 mg for a 70 kg adult is about 0.04 mg/kg body weight and that 3 g is 3,000 mg, which is about 43 mg/kg body weight. Likewise, 10 mg to 1 g (1,000 mg) is a range of 0.14-14 mg/kg body weight, and 5-300 mg is a range of 0.07-4.3 mg/kg body weight. Bolli therefore teaches the claimed macitentan dose ranges.

349. Therefore, Hoeper, Morice, and Bolli render claims 23, 25, 26, 28, 29, 31, 32, 34, 35, 37, 43, 45, 46, 48, 49, 51, 52, 54, 55, and 57 obvious.

(2) PDE5 inhibitor dosage claims 24, 27, 30, 33, 36, 44, 47, 50, 53, and 56

350. Claims 24, 27, 30, 33, 36, 44, 47, 50, 53, and 56 recite:

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

351. Claims 24, 27, 30, 33, and 36 recite a dose range for tadalafil of 0.01 mg to 1 mg per kilogram of patient body weight.

352. Morice teaches administration of 20 mg tadalafil. EX1010, 1. The POSA would have understood the disclosed 20 mg dose encompasses or overlap the ranges of claims 24, 27, 30, 33, and 36, based on different body weights. For example, administering 20 mg to a 70 kg patient equates to 0.29 mg/kg. *Supra* §V11.3, ¶ 167.

353. Additionally, the POSA was knowledgeable of the commonly prescribed and commercially available tadalafil (Cialis®), which the POSA knew to be available in oral tablets in 5 mg, 10 mg, or 20 mg dosages. EX1008, 2. As evidenced by Morice's 20 mg doses, the POSA would use a readily available

tadalafil dosage form. Depending on a patient's weight and the selected Cialis® dosage, the POSA would have understood Hoeper's treatment method, as evidenced by Cialis®, reads on claims 24, 27, 30, 33, and 36. *Supra* §VII.3, ¶¶ 166-68.

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

355. Hoeper teaches administration of 25 mg or 50 mg 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 50 mg to a 70 kg patient equates to 0.71 mg/kg.

356. Additionally, the POSA was knowledgeable of the commonly prescribed and commercially available sildenafil (Viagra®), which the POSA would have known to be available in oral tablets in 25 mg, 50 mg, or 100 mg dosages. EX1007, 1. As evidenced by Hoeper's 25 mg and 50 mg doses, the POSA would have used a readily available sildenafil dosage form. The POSA also knew that sildenafil was commercially available under the brand name Revatio® for PAH in 20 mg oral tablet dosages. EX1025. As evidenced by Hoeper's 25 mg and 50 mg doses, it would have been obvious to the POSA to use a readily available sildenafil dosage form. Depending on a patient's weight and the selected commercially available sildenafil (*i.e.*, Viagra® or Revatio®) dosage, the POSA would have also understood Hoeper's treatment method reads on claims 44, 47, 50, 53, and 56.

357. Accordingly, Hoeper, Morice, and Bolli teach the claimed tadalafil and sildenafil dosages and therefore render claims 24, 27, 30, 33, 36, 44, 47, 50, 53, and of the '847 patent obvious.

D. Keyser does not discourage the POSA from using macitentan.

358. I understand that in the USPTO prosecution history of the '847 patent and in the prosecution history for the related application (*see supra* §VI.A.2), Patent Owner argued that Keyser “teaches away” from using macitentan. Keyser would not have discouraged the POSA from using macitentan in combination with a PDE5 inhibitor to treat a disease such as hypertension or PH. On the contrary, Keyser’s disclosure would have led the POSA to macitentan. I therefore disagree with the arguments that Patent Owner has repeatedly advanced before the Patent Office and the Board. Patent Owner’s characterization of Keyser’s disclosure is flawed and any finding of non-obviousness—including any finding of surprising results—based on Patent Owner’s characterization of Keyser is similarly flawed.

359. Keyser teaches the POSA that endothelin receptor antagonist compounds having IC_{50} values of 10^{-4} mM (*i.e.*, 100 nM) or less have pharmacological utility. *See* EX1005, [049].

360. The POSA would have understood that Example 104 of Bolli’s disclosure is a homolog of macitentan, having an ethyl ($-CH_2CH_3$) R1 group, where macitentan has an n-propyl group ($-CH_2CH_2CH_3$). The structures of Example 104

(EX1004, Table 19 and 20) and macitentan differ only by a single methylene (-CH₂-) and are thus consecutive members in a homologous series. The POSA would have reasonably expected macitentan and the compound of Example 104 to have the same or similar properties, including IC₅₀ values. Example 104 has an ET_A IC₅₀ value of 0.88 nM, which is less than the of 10⁻⁴ mM (*i.e.*, 100 nM) cutoff for pharmacological utility described in Keyser. Accordingly, the POSA would have expected macitentan to have an IC₅₀ value indicating “pharmacological utility” as taught by Keyser, and the POSA would therefore have had reason to combine macitentan with a PDE5 inhibitor as taught by Keyser.

361. Keyser also discloses:

[059] Selective compounds for ET_A antagonists according to this invention, ***in general, should*** display a relative receptor binding ratio of at least 100, such as more than 1000, such as in increments of 500 greater than 1000, *i.e.*, 1500, 2000, 2500, etc., ***if they are going to act at only one of the receptor subtypes, e.g. ET_A.***

[060] Based upon the *in vitro* receptor affinity ratios, bosentan, which is the only endothelin receptor antagonist approved for the treatment of PAH, has an ET_A:ET_B selectivity ratio of 20 and is classified as a nonselective antagonist. In contrast, sitaxsentan has an ET_A:ET_B selectivity ratio of 6500 and is classified as an ET_A-selective antagonist. Therefore, for the purposes of this invention, bosentan or any other non-specific endothelin receptor antagonist would not represent an ET_A-specific antagonist

Id., [059]-[060] (emphases added).

362. Keyser neither states a requirement for a minimum selectivity ratio nor discourages the POSA from using any particular endothelin receptor antagonist

except for, arguably, bosentan or other endothelin receptor antagonists which are no more selective than bosentan for ET_A over ET_B. As is clear, Keyser states that “for the purposes of [Keyser’s] invention, *bosentan or any other non-specific* endothelin receptor antagonist would not represent an ET_A-specific antagonist.” *Id.*, [060] (emphasis added). Keyser thus teaches the POSA to use an endothelin receptor antagonist that is more selective for ET_A than bosentan is, and discourages the use of antagonist that are equal or less selective than bosentan.

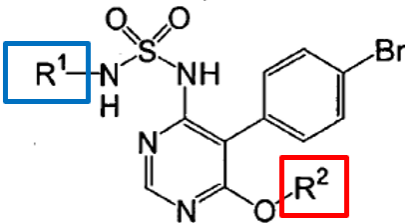
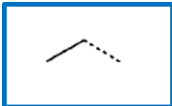
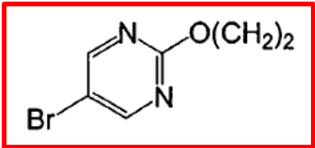
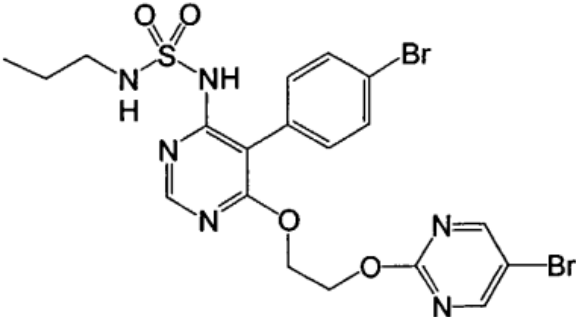
363. As evidenced by the portions of Keyser’s paragraph [059] emphasized above, the POSA would not have regarded Keyser’s discussion of relative receptor binding ratios (*i.e.*, selectivity ratios based on IC₅₀ values) to discourage the POSA from using endothelin receptor antagonists having a relative receptor binding ratio of less than 100, generally. Rather, the POSA would have understood this excerpt from Keyser’s disclosure to merely state a preference and, at most, use an endothelin receptor antagonist which is more selective for ET_A over ET_B than bosentan (which Keyser characterizes as having a selectivity ratio of 20). The POSA, reading Keyser in its entirety, would have understood that Keyser repeatedly uses bosentan and bosentan-containing combination therapies as a baseline. *See, e.g., id.*, [060], [065], Table 4. Thus, the only compounds that Keyser discourages using in its combinations are bosentan and compounds like it. The POSA would not have interpreted Keyser’s unfavorable description of bosentan to extend to macitentan.

Here, neither the “general” guidance in Keyser paragraph [059] nor the statement that a “nonselective antagonist would not function as effectively” in (EX1005, [059], [068]) paragraph [068] would have led the POSA to simply ignore all antagonists with ratios less than 100. Rather, the POSA would have had reason to explore endothelin receptor antagonists having ET_A selectivity ratios of 100 or less. *See, e.g.*, EX1009, EX1010 (disclosing successful combinations using bosentan).

364. Even if Keyser did disfavor endothelin receptor antagonists having ET_A selectivity ratios of less than 100 (which is not how the POSA would have understood Keyser’s teachings), the POSA before or on the ’847 patent priority date would not have been led away from macitentan.

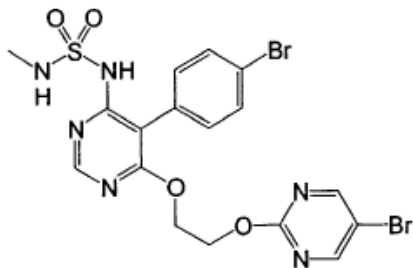
365. The compound of Bolli’s Example 104 has an ET_A IC₅₀ of 0.88 nM and a substantially greater ET_B IC₅₀ of 601 nM, and therefore has a selectivity ratio for ET_A versus ET_B of 683 (*i.e.*, $601 \div 0.88 = 683$). EX1004, 6 (Table 1). The ethyl-containing macitentan homolog of Example 104 thus has a selectivity ratio that is substantially greater than Keyser’s actual minimum of 20 *and* Keyser’s preference for a selectivity ratio of 100. As explained above, the POSA would have expected macitentan, which differs from Example 104 by only a single carbon in a straight-chain alkyl substituent, to have approximately the same biological activity and properties—*e.g.*, ET_A and ET_B IC₅₀ values and ET_A:ET_B selectivity ratio. The structures of Example 104 and macitentan are shown in Table 1 below:

Table 1

Bolli's Example 104 (EX1004, Table 19)	Macitentan (EX1001, claim 1)
General Formula:  Example 104 R Groups:  	

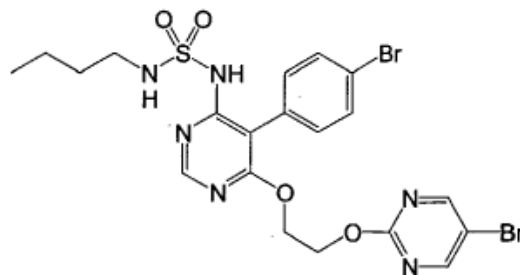
366. Bolli also discloses the methyl and butyl homologs of macitentan and Example 104 as preferred compounds, reproduced below:

Methyl Homolog of Macitentan



EX1004, 29 (left column, third structure)

Butyl Homolog of Macitentan



EX1004, 27 (right column, fourth structure)

367. Bolli thus teaches a full homologous series of compounds having straight-chain alkyl substituents of one, two, three, and four carbons in length, each as a “preferred” compound for use as a therapy for diseases involving vasoconstriction (*e.g.*, hypertension or PH). *See* EX1004, 25 (“Another group of preferred compounds is depicted below”), 40 (“The following examples illustrate the invention.”), 94 (Table 19). The POSA would have understood that the Bolli inventors regarded this entire homologous series as representing promising, potent, and interchangeable compounds for treatment of, *e.g.*, hypertension or PH. The POSA would thus have expected these homologs to have similar potencies and selectivities for endothelin receptors. Thus, even if the POSA were to interpret Keyser’s paragraph [059] as disfavoring any particular antagonists, the POSA would still not have been discouraged from using macitentan or any of the macitentan homologs taught by Bolli.

368. I also understand that Patent Owner has attempted to rely on data set forth in papers published after the filing of the patent application which was granted as the ’847 patent. The first of these publications, which is by Iglarz *et al.* and published in 2008, provides *in vivo* data which Patent Owner has cited to argue that macitentan is a nonselective ET antagonist. *See* EX1006, 386. However, even if the POSA were to ignore the *in vitro* nature of the selectivity guidance provided in Keyser, and rely instead on Iglarz’s *in vivo* data, the POSA would still not be

surprised by the results of the macitentan-PDE5 combination disclosed and made obvious by the prior art. Iglarz discloses a selectivity ratio for macitentan of 1:782 in favor of ET_A. EX1006, 385; EX1011, 6 (describing an IC₅₀ of 0.5 for ET_A and 391 for ET_B). These ratios both exceed the alleged “requirement” in Keyser that selectivity ratio exceed 100. EX1005, [059]. Thus, Patent Owner’s post-priority reference, Iglarz, confirms the ET_A-selectivity of macitentan. Therefore, even if the POSA had access to Iglarz, they would not have been surprised by the alleged synergistic effects. 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.*, 9.⁴ Iglarz explains, citing several pre-priority references, that dual antagonists are more effective in humans with disease. *Id.* Thus, if the information in Iglarz may be considered even though it

⁴ 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. EX1011, 7. Macitentan was “10-fold more potent” and had “2-fold longer duration of action than bosentan.” *Id.*

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 disease, 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 above). If anything, Iglarz would increase the POSA’s expectation of efficacy *because* it also teaches that dual antagonists are more effective *in vivo*. Despite the clear *in vitro* data, Patent Owner has asserted that Iglarz shows that the ET_A/ET_B selectivity for macitentan is “only 50:1.” EX1006, 386. Patent Owner’s purported ratio is presumably based on *in vivo* data, however, and would not have deterred the POSA.

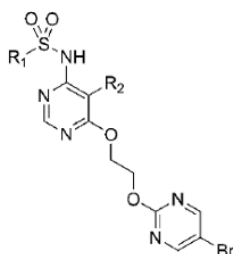
369. Furthermore, I understand that Patent Owner has cited a publication by Bolli *et al.*, (“Bolli 2012”) as part of an argument that the POSA would have understood macitentan to be a dual antagonist. *See* EX1024. Bolli 2012 bears a publication date in 2012, however, so it was published after the ’847 patent priority date. Thus, it would not have been available to the POSA and based on my understanding of the law from counsel, it should therefore not be part of a patentability analysis.

370. In any event, even if the POSA had access to Bolli 2012 during the relevant timeframe before the priority date, the POSA still would have regarded macitentan as a highly potent and selective ET_A receptor antagonist from the data

presented in Bolli 2012. Specifically, Table 6 of Bolli 2012 provides ET_A and ET_B IC₅₀ values for various compounds, including macitentan (compound 17) and three of its homologs (compounds 60, 61, and 62). *See id.*, 6 (Table 6, reproduced and annotated below).

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Table 6. Optimization of the Sulfamide Moiety^a

compd	R ₁	R ₂	IC ₅₀ ET _A ^b [nM]	IC ₅₀ ET _B ^b [nM]	max ΔMAP ^c [mmHg]	ABC ^d [mm Hg·h] (n)
57	benzyl-NH-	4-bromophenyl	1.6	461	-14 ± 3	-445 (6)
60	methyl-NH-	4-bromophenyl	1.7	812	-21 ± 6	-1045 (5)
61	ethyl-NH-	4-bromophenyl	0.8	830	-20 ± 10	-598 (6)
17	<i>n</i> -propyl-NH-	4-bromophenyl	0.5	391	-25 ± 6	-922 (6)
62	<i>n</i> -butyl-NH-	4-bromophenyl	0.3	158	-16 ± 4	-443 (5)
63	cyclopropyl-NH-	4-bromophenyl	4.4	1474	nd	nd
64	<i>N</i> -benzyl-methyl- <i>N</i> -	4-bromophenyl	4.3	5208	nd	nd
65	morpholino	4-bromophenyl	2.8	2829	nd	nd
66	<i>n</i> -propyl-NH-	4-chlorophenyl	1.2	784	nd	nd
67	<i>n</i> -propyl-NH-	3-methoxyphenoxy	1.9	468	-15 ± 3	-391 (6)
68	<i>n</i> -propyl-NH-	6-chloro-3-methoxyphenoxy	0.4	208	-21 ± 5	-500 (6)
69	<i>n</i> -propyl	4-bromophenyl	2.2	3058	-25 ± 4	-1116 (6)
70	<i>n</i> -butyl	4-bromophenyl	1.1	2424	-22 ± 3	-734 (5)

^aNote that compounds 17, 57, and 60–68 represent sulfamides, while compounds 69 and 70 are sulfonamides. ^bIC₅₀ values as determined in binding assays using membranes of Chinese hamster ovary (CHO) cells containing either the recombinant ET_A or ET_B receptor, respectively. Data are given as geometric means of at least three independent measurements. ^cMaximal mean arterial blood pressure reduction as extracted from the moving average over 6 h. ^dArea between curve (ABC) as calculated from the blood pressure recordings 24 h before and after administration of 3 mg/kg of the compound to conscious hypertensive Dahl salt-sensitive rats; max ΔMAP = maximal reduction in mean arterial blood pressure; n = number of animals in the experiment; nd = not determined.

371. The ET_A and ET_B IC₅₀ values in the Bolli 2012 paper are also consistent with the POSA's expectation of macitentan based on the data provided by Bolli (EX1004) for the ethyl homolog of Example 104.

372. In fact, Table 6 from Bolli 2012 provides ET_A and ET_B IC₅₀ values for the entire homologous series of macitentan and its methyl- (compound 60), ethyl-

(compound 61), and n-butyl (compound 62) substituted homologs. As explained above, this entire homologous series are preferred compounds taught by Bolli. *See supra* §V.D.1. Notably, the ethyl homolog identified as compound 61 in Bolli 2012 is described as having ET_A and ET_B IC₅₀ values of 0.8 nM and 830 nM, respectively, and thus an ET_A:ET_B selectivity ratio of 1,037.5 (*i.e.*, $830 \div 0.8 = 1,037.5$). Macitentan with a selectivity ratio of 782 ($391/0.5$), similar to that of compound 61, as taught by Bolli and understood by the POSA, are both selective endothelin receptor antagonists that preferentially “block/inhibit/antagonize” ET_A receptors to a much greater degree than ET_B receptors.

373. To the extent Patent Owner chooses to characterize macitentan or any of its homologous ET_A antagonists as dual antagonists, such a characterization is merely subjective and ignores the explicit disclosure of Keyser. Example 104 clearly possesses a level of selectivity as preferred by Keyser, and the POSA would have expected macitentan to have similar selectivity. And, as confirmed by Bolli 2012, the entire C₁-C₄ homologous series taught by Bolli possesses high ET_A selectivity.

374. Further still, Bolli 2012 describes bosentan as a “dual ET_A/ET_B receptor antagonist” having an ET_A IC₅₀ of 45 nM and an ET_B IC₅₀ of 202 nM, and thus an ET_A:ET_B selectivity ratio of only 4.49 (*i.e.*, $202 \div 45 = 4.49$), which is substantially lower than the selectivity ratio of 782 disclosed by Bolli 2012 for macitentan. The POSA would thus not have regarded macitentan to be a “dual” antagonist like

bosentan. As I explain above, the POSA would have, in fact, understood macitentan to be a selective ET_A antagonist based on Bolli. Moreover, even when considering post-priority publications cited by the Patent Owner, which would not have impacted the POSA's understanding at the relevant time—the POSA would still have concluded that macitentan was a potent ET_A antagonist.

E. Any synergism resulting from a combination of macitentan and a PDE5 inhibitor would not have been surprising to the POSA.

375. I also understand that the Patent Owner asserts that surprising results of “synergistic effect” justify nonobviousness. *E.g.*, EX1001, 7:19; EX1003, 9-10; EX1006, 88-89. I disagree. The POSA would not have been surprised by any synergism achieved by the combination of macitentan and a PDE5 inhibitor as claimed by the '847 patent.

376. Considering Bolli's disclosure that macitentan may be administered in combination with one or more vasodilators, synergism with PDE5 inhibitors would have been reasonably expected by the POSA in view of the disparate and beneficial mechanisms of action of these two drug classes discussed previously to relieve vasoconstriction (ET-1 receptor antagonism) and induce vasodilation (PDE5 inhibition to preserve endogenous nitric oxide).

377. The POSA would have understood that pharmacological synergism, also known as supra-additivity, occurs when a mixture of two or more drugs produces a greater response than expected (*i.e.*, greater than the sum of their

individual effects). Drug synergism can be expected when drugs which act by different mechanisms of action are co-administered.

378. For example, “[i]f mechanisms of action [“MOA”] are not well understood or if the model is inappropriate, the effect of a combination of agents may well be unexpected. Then, with increasing understanding of the agents, the model is progressively modified so as to fit the observed effect, and the effect becomes what is expected.” EX1034, 3. In this case, the MOAs for endothelin receptor antagonists and PDE5 inhibitors were well understood by the POSA as of the priority date.

379. Further, “[a] combination of agents is said to show interaction when the magnitude of its effect is greater or smaller than expected, expectation being based on the dose-effect relations of the individual agents in the combination. The crux of the matter is to decide what is expected, and various rules have been proposed to this end (for example, that the expected effect is the sum of the effects of the individual constituents of the combination, or that it is the product of these effects, or that it may be calculated from the law of mass action).” EX1040, 1.

380. The POSA would also have understood that “[t]he interpretation of the impact of both qualitative and quantitative measures of agent interaction is dependent upon the field of application.” EX1035, 2.

381. As of the assumed priority date, the mechanisms of action of endothelin

antagonists (EX1003; EX1027) and PDE5 inhibitors (EX1007; EX1008) were well known. Thus, at that time, the POSA would not have been surprised that the combination of an endothelin antagonist and a PDE5 inhibitor would have a synergistic effect on lowering blood pressure. Endothelin antagonism removes one of the most potent vasoconstrictors known from exerting its effects on blood vessels and enhancement of endogenous nitric oxide by PDE5 inhibition and provides enhanced levels of cGMP, one of the most potent blood vessel vasodilators known. It is not surprising that this combination would have effects on blood pressure greater than either agent utilized alone, *e.g.*, supra-additive effects or synergism when combined.

382. Synergy is also achieved by the dual antagonism of ET-1 receptors on smooth muscle cells from airways and blood vessels resulting in concomitant enhanced airway and blood flow. The POSA would have had reason to expect that macitentan, unlike, for example, calcium channel blockers, would produce synergy with a PDE5 inhibitor. Macitentan and calcium channel blockers both result in decreased intracellular calcium which relaxes vascular smooth muscle and induces vasodilation. *See* EX1039, 1. However, the combination of ET_A antagonism and calcium channel blockade would not benefit from the action of nitric oxide, generated by PDE5 inhibition, to induce vasodilation and improve hemodynamics (*i.e.*, lower vascular resistance and decreased pulmonary and arterial blood pressure).

Considering simultaneous antagonism of two vasoconstrictive pathways (endothelin and calcium channels), the most the POSA would have expected from a combination of a calcium channel blocker and a PDE5 inhibitor is an additive effect on pulmonary or arterial blood pressure lowering.

383. However, the POSA would also have recognized that the combination of macitentan and a PDE5 inhibitor would be the preferred combination due to not only the presence of ET_A receptors on both airways and vascular smooth muscle cells in the pulmonary circulation (lung) but also PDE5 enzyme in high concentrations in vascular smooth muscle cells. *See, e.g.*, EX1030, 1-2; EX1036, 1. The ability to antagonize both airway and smooth muscle ET_A receptors with ET_A antagonists would have been highly apparent to the POSA as targets in treatment of PH considering that vasoconstrictive endothelin ET-1 is synthesized and released by airway epithelial and vascular endothelial cells. *See, e.g.*, EX1030, 1.

384. Prevention of airway smooth muscle cell contraction, similar to vascular smooth muscle cell contraction, leads to vasodilation of the bronchial and blood vessel smooth muscle, respectively, such that both airflow and blood flow increase. Thus, an ET_A antagonist, when administered as a single medication, would have been expected by the POSA to have positive effects on pulmonary and cardiac hemodynamics. Improving the hemodynamic status of a patient would be expected to lead to normalization of oxygenation levels.

385. Oxygenation is determined by the ratio of blood flow to airflow at the capillary/alveoli level of the lung. Mismatch in either airway flow or blood flow can result in dramatic changes in pulmonary pressures and slowly impede the ability to breathe.

386. As pulmonary pressures rise, it becomes harder for the heart to pump blood to the lungs and thus cardiac work is increased.

387. The POSA would have recognized that dual mechanisms of action may improve overall efficacy of many complex diseases, especially those involving the interplay of respiratory and circulatory systems. It would be completely reasonable to expect that improving pulmonary and cardiac hemodynamics and enhancing oxygenation, through a combination of endothelin antagonism and PDE5 inhibition, may further reduce the symptoms of PAH or systemic hypertension than achieved with endothelin ET_A receptor antagonism alone or with PDE5 inhibition alone.

388. The POSA would also have recognized that PDE5 is a highly specific enzyme that is present in lung tissue, mainly in the pulmonary vessel smooth muscle as well as in pulmonary artery endothelial cells. *See, e.g.*, EX1036.

389. The POSA would also have recognized that the receptors for endothelin and the PDE5 enzyme are associated with similar cell types (smooth muscle cells) in the lung and pharmacological approaches directed at these targets may result in at least additive effect but certainly could be synergistic due to highly distinct

mechanisms of action, both resulting in expected positive hemodynamic outcomes.

390. Thus, the POSA would have expected pharmacological synergy to decrease pulmonary and arterial blood pressure and other hemodynamics when two disparate mechanisms are operating, one to prevent vascular and airway vasoconstriction (*i.e.*, ET_A receptor antagonism) and another to elicit vascular vasodilation by either receptor-mediated elaboration of endothelial derived nitric oxide or preventing its degradation by PDE5 inhibition. Pharmacological synergism generally results when disparate mechanisms are at work. Similar mechanisms (blocking vasoconstriction) result in additive effects. Disparate mechanisms (*i.e.*, blocking vasoconstriction and inducing vasodilation) generally would be expected to result in supra-additivity or synergism. For example, the POSA would have understood from Hoeper that, 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. The POSA would also have understood that Morice describes how bosentan combined with sildenafil caused exercise tolerance to “double[]”, and that changing to tadalafil had an excellent symptomatic response. EX1010, 1. In fact, as Lunze *et al.* demonstrated, the combination of bosentan and sildenafil proved to be safe and effective in improving clinical and hemodynamic parameters in patients with PAH, and reasoned that “[it] is clear 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 and mode of drug delivery while minimizing side effects.” EX1014, 1-2.

391. As explained above, the biological pathways implicated by endothelin receptor antagonists, including macitentan, and PDE5 inhibitors are complementary.

392. As I also explain above, the POSA would have known that blocking the ET_A receptor with an endothelin receptor antagonist would help prevent vasoconstriction in patients with hypertension or PH to increase blood flow and reduce pulmonary pressure. The POSA also would have also understood that PDE5 inhibition (by, *e.g.*, sildenafil or tadalafil) causes cGMP levels to rise, leading to smooth muscle relaxation and vasodilation, thereby reducing pulmonary artery pressure and improving blood flow.

393. The POSA would have reasonably expected drugs belonging to the same class (*e.g.*, two PDE5 inhibitors) to exert merely additive effects as they have similar therapeutic mechanisms of action. That is not the case here.

394. The POSA would have understood a combination therapy comprising an endothelin antagonist and a PDE5 inhibitor to target two distinct pathways involved in vascular tone regulation and would have therefore reasonably expected such a combination of drugs to be complementary to exhibit synergy. The endothelin receptor (type A) antagonist directly blocks the vasoconstrictive effect of ET-1,

while the PDE5 inhibitor enhances the vasodilatory effects of cGMP.

395. The POSA might have reasonably expected a non-selective type A and B vascular smooth muscle endothelin receptor antagonist such as bosentan to hinder the beneficial effect of enhanced nitric oxide levels on blood pressure lowering due to concomitant endothelial ET_B receptor blockade. However, a non-selective endothelin antagonist, bosentan, was approved by the FDA for PAH in 2001. *See, e.g.,* EX1038, 1.

396. The POSA would have reasonably expected a drug combination targeting two distinct mechanisms of vascular and airway reactivity to provide a synergistic effect on pulmonary or arterial blood pressure. Eliminating smooth muscle vasoconstriction (on blood vessels and airways) with an ET antagonist reduces vasoconstrictive intracellular calcium and enhancing vasodilation with a PDE5 inhibitor by preserving endogenous vasodilatory nitric oxide, provides disparate mechanisms of action. The endpoint cellular effectors—lowering intracellular calcium by ET antagonism and enhancing cGMP levels by PDE5 inhibition—would be expected to have a net synergistic effect to lower vascular resistance and thus lower pulmonary and arterial blood pressures.

397. The POSA would have reasonably expected the claimed drug combinations of the '847 patent to reduce pulmonary blood pressure to an extent greater than the sum of the effects of an endothelin receptor antagonist alone and a

PDE5 inhibitor alone.

398. I understand from counsel that if synergy is expected, it cannot overcome obviousness. Even if the combinations claimed by the '847 patent produced any synergistic results, such results would have been expected. Accordingly, the claims of the '847 patent would have been obvious based on the disclosures of Bolli and Keyser.

F. The '847 patent claims do not require any surprising effect, nor are they commensurate with Patent Owner's alleged surprising effect.

399. I understand from counsel that surprising results must be commensurate with the claims if the results are to justify nonobviousness of a combination otherwise disclosed in the prior art. Here, the '847 patent claims do not recite or otherwise define a surprising effect which the claimed products, pharmaceutical compositions, or methods can achieve. Moreover, the '847 patent claims are not commensurate with any hypothetical surprising effect, including any of the data provided in the '847 patent specification, which the POSA would not consider to support or define a surprising effect or result. In fact, Patent Owner's alleged evidence of unexpected results—which the POSA would not have found to be surprising—in the patent specification is incredibly narrow. 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 route of administration at the same time). The claims’ scope has no relation to the Examples. 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. For example:

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

The claims include:	But the Examples describe only:
Udenafil as the PDE5 inhibitor (claims 1-2, 5-7, 10-11)	No disclosure
Any administration timing: simultaneous, separate, or “over a period of time” (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)	0.3 mg/kg
Any dose of macitentan within 0.05-2 mg/kg (claims 23-24, 26-27, 29-30, 32-33, 35- 36, 43-44, 46-47, 49-50, 52-53, 55-56)	0.3 mg/kg

The claims include:	But the Examples describe only:
Any dose of macitentan within 0.1-1 mg/kg (claims 25, 28, 31, 34, 37, 45, 48, 51, 54, 57)	0.3 mg/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)	10 mg/kg
Any dose of tadalafil within 0.01-1 mg/kg (claims 24, 27, 30, 33, 36)	10 mg/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)	30 mg/kg
Any dose of sildenafil within 0.1-2 mg/kg (claims 44, 47, 50, 53, 56)	30 mg/kg
Any disease wherein vasoconstriction is involved (claims 1-4, 6-9)	Dahl-sensitive rats that develop hypertension upon salt intake and spontaneously hypertensive rats

The claims include:	But the Examples describe only:
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.

400. Setting aside whether the examples of the '847 patent define a surprising effect (they do not), the data presented in Examples 1-3 were obtained from administration of macitentan and either tadalafil or sildenafil in mg/kg body weight dosages that are not reflected in the '847 patent claims. Examples 1 and 2 both explain that their data were obtained by administering 0.3 mg/kg macitentan and 10 mg/kg tadalafil. EX1001, 6:54-7:7. The data of Example 3 were obtained by administering 0.3 mg/kg macitentan and 30 mg/kg sildenafil. *Id.*, 7:15-19.

	Macitentan “0.05 mg to 2 mg [or] 0.1-1 mg per kg of patient body weight”	Tadalafil “0.01 mg to 1 mg per kg of patient body weight”	Sildenafil “0.1 mg to 2 mg per kg of patient body weight”
Example 1	0.3 mg/kg	10 mg/kg	-
Example 2	0.3 mg/kg	10 mg/kg	-
Example 3	0.3 mg/kg	-	30 mg/kg

401. No claim of the '847 patent is commensurate with or limited to the

dosages from the Examples.

402. Independent claim 1 does not define a therapeutic effect to be achieved, nor does claim 1 recite any dosages for either macitentan or the PDE5 inhibitor. The POSA would have understood it to cover an infinitely broad range of dosages for both macitentan and the PDE5 inhibitor and would thus understand that claim 1 is not commensurate with any purported results or technical effects, surprising or otherwise. Put another way, the patent does not describe the “synergy” it describes for all doses. For example, claim 1 lacks any express limitations regarding (1) treatment effect—*e.g.*, a level of reduction in blood pressure or other quantitative or even qualitative effect—achieved by the claimed combination product; (2) who can be treated (humans or animals—rats or otherwise); (3) dosage; (4) specific PDE5 inhibitors; (5) treatment frequency/timing (*e.g.*, simultaneous, separate, or over a period of time); (6) whether the disease/condition is chronic or acute; or (7) what specific disease is being treated.

403. With respect to dosages which are actually recited in the claims, macitentan dosages are only claimed in claims 23, 25, 26, 28, 29, 31, 32, 34, 35, 37, 38, 45, 46, 48, 49, 51, 52, 54, 55, and 57 in ranges of either (i) 0.05 mg to 2 mg per kilogram of patient body weight or (ii) 0.1 mg to 1 mg per kilogram of patient body weight. These claims define ranges that are not commensurate with the singular dosage of the Examples (*i.e.*, 0.3 mg/kg body weight). The Examples of the '847

patent do not provide data across the whole range of claimed macitentan dosages.

404. Similarly, the claims reciting dosage ranges of tadalafil (*i.e.*, claims 24, 27, 30, 33, and 36) are not commensurate with any of the data provided in the '847 patent. These claims recite a range of 0.01 mg to 1 mg tadalafil per kilogram of patient body weight. Examples 1 and 2 only provide data for administration of 10 mg tadalafil per kg body weight, which falls far outside the claimed range.

405. Likewise, the claims reciting dosage ranges of sildenafil (*i.e.*, claims 44, 47, 50, 53, and 56) are not commensurate with any of the data provided in the '847 patent. These claims recite a range of 0.1 mg to 2 mg sildenafil per kilogram of patient body weight. Example 3 only provides data for administration of 30 mg sildenafil per kg body weight, which falls far outside the claimed range.

	Dosages from Examples 1-3 of the '847 patent	Dosage ranges specified in the '847 patent claims
Macitentan	0.3 mg/kg	0.05 mg/kg to 2 mg/kg or 0.1 mg/kg to 1 mg/kg
Tadalafil	10 mg/kg	0.01 mg/kg to 1 mg/kg
Sildenafil	30 mg/kg	0.1 mg/kg to 2 mg/kg

406. A single dosage of macitentan cannot support the full range specified in any of the dependent claims, which span from 0.05 mg/kg to 2 mg/kg or from 0.1

mg/kg to 1 mg/kg. The POSA would not reasonably consider the full ranges of claimed macitentan dosages to be supported by a single data point of 0.3 mg/kg.

407. In any event, the fact that the singular macitentan dose of the Examples falls within the narrowed macitentan ranges of the patent claims is irrelevant. This is because the only data points for tadalafil and sildenafil, which must be combined with macitentan, fall *far* outside any claimed ranges for either claimed PDE5 inhibitor. As I explain above, the patent Examples only address a 10 mg/kg tadalafil dose and a 30 mg/kg sildenafil dose. The amount of tadalafil used in the Examples is *ten times* the amount permitted by the dosage range specified in dependent claims 24, 27, 30, 33, and 36. Likewise, the single sildenafil dose of 30 mg/kg is *fifteen times* the upper end of the sildenafil range of dependent claims 44, 47, 50, 53, and 56. Here, there are dozens of claims directed to macitentan doses (0.5-2 mg/kg), tadalafil doses (0.1-1 mg/kg), and sildenafil doses (0.1-2 mg/kg). The Examples' disclosure of 0.3 mg/kg, 10 mg/kg, and 30 mg/kg doses, respectively, does not support, let alone fully support, these dependent claims (and claim 1 is even broader, unlimited by dosage). Regarding timing of administration, claim 1, for example, appears to encompass administration, in any conceivable amount, of a first compound for months or even years before administration of the second compound. Such boundless claim language simply cannot be commensurate with Patent Owner's alleged results, unexpected or otherwise.

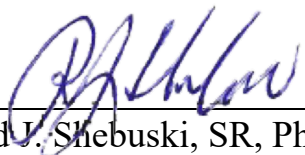
408. Moreover, as I explain above in section VI.B.1.d, the data presented in Examples 1-3 of the '847 patent are thus insufficient to convey to the POSA that surprising synergism was in fact exhibited or observed. The specification discloses results from an unknown number of rats, with no placebo control or statistical analysis, at one dosage of macitentan (0.3 mg/kg) or one dose of tadalafil (10 mg/kg) or sildenafil (30 mg/kg). EX1001, 6:52-7:19; *see also supra* §VI.B.1.d. The rats were salt-sensitive or spontaneously hypertensive rats. *Id.*, 5:15-20.

409. Accordingly, none of the '847 patent claims are commensurate with any of the data presented in the '847 patent specification, let alone any surprising results, which are neither described by, nor reasonably inferred from, the '847 patent.

VIII. Conclusion

410. For the reasons described and explained above, claims 1-57 of the '847 patent are anticipated by Bolli and would have been obvious to the POSA in view of Bolli and Keyser, and in view of Hoeper, Morice, and Bolli.

411. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001 and that such willful false statements may jeopardize the validity of the above-identified patent.



Ronald J. Shebuski, SR, Ph.D.

June 10, 2025

Date

APPENDIX A

CURRICULUM VITAE
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CONTACT INFORMATION

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PERSONAL

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EDUCATION

1981-1985 **University of Minnesota-Mpls**, PhD, Pharmacology
1971-1976 **University of Wisconsin-Madison**, BS, Microbiology

PHARMA and BIOTECH EXPERIENCE

2022-present President & CEO
Nytrix, Inc., Athens, GA

1998-present Private Consultant to Pharma and Biotech Industry
Cardiovascular Research Consulting, LLC

2010-2020 President & CEO
Cylerus, Inc., Melbourne, FL

2002-2005 VP, R&D
Afmedica, Inc., Kalamazoo, MI

1998-2002 VP, R&D
CarePoint Medical, Inc., Eden Prairie, MN

1990-1998 Director, Cardiovascular Pharmacology
Pharmacia & Upjohn, Inc., Kalamazoo, MI

1988-1990 Senior Research Fellow, Department of Pharmacology
Merck Sharp & Dohme Research Laboratories, Inc.,
West Point, PA

1985-1988 Senior Investigator, Cardiovascular Pharmacology,
Smith Kline & French Laboratories, Inc., K of P, PA

ACADEMIC APPOINTMENTS

2000-2010	Adjunct Associate Professor Department of Pharmacology University of Minnesota Medical School Minneapolis, MN
2005-2010	Adjunct Professor Department of Integrative Biology & Physiology University of Minnesota Medical School Minneapolis, MN
1992-2000	Adjunct Associate Professor Department of Pharmacology University of Michigan Medical School , Ann Arbor, MI

OTHER APPOINTMENTS

2009-2017	Special Government Employee (SGE, Grade 15, Step 10) FDA/CDER-CV/Renal Division , Bethesda, MD
2005-2017	General Partner Apjohn Group, LLC , Kalamazoo, MI Life Sciences Business Accelerator

CONSULTING CLIENTS (2006-present)

-Abbott Laboratories, Inc., Abbott Park, IL (2009-2010)
(Consultant for Safety Pharmacology group on oncology drug with potential pro-platelet aggregatory activity).

-Accord Biomaterials, Inc., Ann Arbor, MI (2008-2011)
(Retained consultant to provide direction on coating medical devices with anti-microbial and anti-platelet platelet surfaces)

-Ariad Pharmaceuticals, Cambridge, MA (2014-2015)
(Retained hematology/pharmacology consultant to ponatinib project)

-BioMarin, Novato, CA (2010-2012)
(Hourly consultant on external drug development projects)

-InspiRx, Inc., Durham, NC (2015-2021)
(Retained consultant on inhaled interferon gamma for IPF)

-Medivas, Inc., San Diego, CA (2007-2008)
(Retained consultant on drug-eluting polymers for vascular graft failure)

-Medrad/Possis (Division of Bayer, Inc.), Minneapolis, MN and Pittsburgh, PA (2008-2012)
(Retained consultant on drug-eluting angioplasty balloons)

-Mercator Medsystems, Inc., San Leandro, CA (2006-2008)
(Retained consultant on drug delivery to adventitial surface of blood vessels)

-NetScientific, London, UK (2022-present)
(Retained consultant on novel thrombolytic drug for PE and stroke)

-Nostrum Pharmaceuticals/Symmetrix Biotech, Inc., Edison, NJ (2008-2021)
(Retained consultant on novel thrombolytic drug development)

-Proteos, Inc., Kalamazoo, MI (2010-2013)
(Retained consultant on peptide-based PTH analogs)

-SWMF, Kalamazoo, MI (2006-2012)
(Hourly consultant to SWMF Venture Capital group to review CV opportunities when requested)

-Vascular Magnetics, Philadelphia, PA (2012-2014)
(Retained consultant on local treatment of PAD with paclitaxel)

INTELLECTUAL PROPERTY EXPERT WITNESS EXPERIENCE (2010-PRESENT)

-Saffran vs. J&J Cordis (2010-2011)

Retained as testifying expert witness by Dickstein Shapiro, LLP on behalf of Bruce N. Saffran, M.D., Ph.D., in Saffran vs. J&J Corporation et al., 2:07-CV-451 (TJW), US District Court, E.D., Texas, to analyze technical information regarding to the pharmacokinetics of drug release from certain J&J and Cordis Corp. products and technical information, US patent #5,653,760. **Deposed and Jury Trial**

-Sanofi-BMS vs. Apotex (2010-2011)

Retained as testifying expert witness by Gowlings, Lafleur, Henderson, LLP, Toronto, Canada on behalf of Sanofi-BMS in Sanofi-BMS vs. Apotex, Ottawa, Canada to analyze technical information regarding to the anti-platelet drug Plavix[®] and technical information, Canadian patent #1,336,777. **Deposed and Bench Trial**

-Cook Medical vs. Medrad, PA (2011)

Retained as testifying expert witness by Medrad Inc., in Cook Medical vs. Medrad to analyze technical information regarding to drug-eluting medical devices, US patent # 7,803,149.

-Saffran vs. Abbott (2011)

Retained as testifying expert witness by Dickstein Shapiro, LLP on behalf of Bruce N. Saffran, M.D., Ph.D., in Saffran vs. Abbott Corporation to analyze technical information regarding to the pharmacokinetics of the release of drug from certain Abbott products and technical information, US patent #5,653,760.

-Schering Merck vs. Mylan, New York, NY (2011)

Retained as testifying expert witness by Sidley Austin, LLP, New York, NY on behalf of Schering Merck in Schering Merck vs. Mylan to analyze technical information regarding to drugs for treating and preventing atherosclerosis, US patent # 5,846,966.

-Sanofi vs. Amphastar (2013-2014)

Retained as testifying expert witness by Gibson Dunn & Crutcher on behalf of Sanofi to analyze technical information regarding to Lovenox bioequivalence, US patent # 5,389,618. **Deposed**

-Boehringer Ingelheim vs. Apotex (2016)

Retained as testifying expert witness by Cozen O'Connor on behalf of Apotex to analyze technical information regarding to Pradaxa, US patent # 6,087,380. **Deposed and Bench Trial**

-United Therapeutics Corp. (UTC) vs. Waston/Actavis (2016-2017)

Retained as testifying expert witness by WSGR on behalf of UTC to analyze technical information regarding US patents 8,410,169, 8,747,897, 9,278,901, 9,393,293 and 9,422,223. **Deposed**

-Eli Lilly vs. Apotex (2017)

Retained as testifying expert witness by Belmore Neidrauer (Toronto) on behalf of Eli Lilly to analyze technical information regarding US Patent # 2,432,644.

-Bayer vs. Aurobindo (2017)

Retained as testifying expert witness by Shaw Keller on behalf of Aurobindo to analyze technical information regarding US Patent #7,157,456. **Deposed**

--Grellner vs. Raabe (2016-2018)

Retained as testifying expert witness by Nix, Patterson & Roach on behalf of Grellner to analyze technical information regarding VenaSeal, US Patent # 8,475,492.

-Mass Tort vs. Pfizer (2017-2018)

Retained as testifying expert witness by DLA Piper on behalf of Pfizer to analyze technical information regarding the pharmacokinetics of sildenafil (Viagra).

-BMS Canada Co and BMS Holdings Ireland Unlimited Company vs. Apotex Inc. (2019)

Retained as testifying expert witness by Goodman's LLP on behalf of BMS to analyze technical information regarding to factor Xa. Canadian Patent 2,461,202. **Deposed**

- Sanofi, Bristol-Myers Squibb (2019)

Retained as testifying expert witness by McCarthy Tetrault LLP on behalf of Sanofi/Bristol-Myers Squibb regarding Canadian litigation involving Clopidogrel (Plavix).

-Novartis vs. Alembic (2021)

Retained as testifying expert witness by Venable Law on behalf of Novartis regarding Entresto.

-UTC/Supernus vs. ANI (2022)

Retained as testifying expert witness by McDermott, Will & Emery on behalf of UTC/Supernus regarding Treprostinil. US Patent 9,278,901.

-GW Pharmaceuticals LTD vs. Otsuka LTD (2022)

Retained as testifying expert witness by Williams & Connolly LLP on behalf of GW Pharma regarding Epidiolex.

-Pfizer, Inc. vs. Regor Therapeutics, Inc. (2022-2023)

Retained as testifying expert witness by Quinn Emanuel on behalf of Regor Therapeutics regarding GLP-1 agonists for diabetes.

-United Therapeutics vs. Janssen/Actelion (2025)

Retained as testifying expert witness by McDermott, Will & Emery on behalf of United Therapeutics regarding combination treatments for pulmonary hypertension.

AWARDS

- | | |
|------|--|
| 1984 | Travel Award, Graduate Student, American Society for Pharmacology and Experimental Therapeutics, Annual Meeting, Indianapolis, Indiana |
| 1985 | Bacaner Basic Science Research Award for Outstanding Graduate Research in Pharmacology - University of Minnesota, Minneapolis, Minnesota |
| 1994 | 1st Annual F.E. Shideman Distinguished Alumnus Award
University of Minnesota, Department of Pharmacology, Minneapolis, Minnesota |

THESIS

Influence of Alpha-1 Adrenoceptor Antagonists in the Central Regulation of Blood Pressure and Cardiovascular Reflexes. Submitted to the Faculty of the Graduate School of the University of Minnesota in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy, 1985.

AFFILIATIONS

American Association for the Advancement of Science
American Heart Association
American Society for Pharmacology and Experimental Therapeutics
New York Academy of Sciences
Thrombosis Council - American Heart Association

EDITORIAL BOARDS

Expert Opinion on Investigational Drugs (Section Editor, CV and Renal)
Research Communications in Pharmacology and Toxicology, (Section Editor, CV Pharmacology)
Journal of Pharmacology and Experimental Therapeutics
Current Opinion in Pharmacology (CV/Renal Editor)

REVIEWER FOR

Journal of Biochemical Pharmacology
Journal of Cardiovascular Pharmacology
Journal of Pharmacology and Experimental Therapeutics
Circulation
Blood
Cardiovascular Research
American Journal of Physiology
British Journal of Pharmacology

GRANT REVIEW COMMITTEES

Texas Technological Grants - 1989
Special NIH Study Section - Small Business Innovative Research Grants (SBIR) - 1991
Research Grant Committee, American Heart Association of Michigan - 1992-1995
North Carolina Biotechnology Center - 1995
Department of Veterans Affairs - 1995
NIH Study Section/Thrombosis (NHLBI) - 2004
NIH Study Section/Integrative Pharmacology (NIGMS) - 2004
SBIR/STTR Study Section - 2012
SBIR/STTR CV/Hematology Study Section - 2014-2024

OTHER COMMITTEES

ASPET Program Committee - 1992-1995, Reappointed for Term 1995-1997
ASPET Finance Committee- 1998-2002
Founder and Chairman , ASPET Division for Drug Discovery, Drug Development and Regulatory Affairs – 1999-2001

TEACHING ACTIVITIES

University of Minnesota

Medical School Pharmacology, Laboratory Teaching Assistant, 1981-1985
Invited Graduate Lectures, Department of Pharmacology, 2000-2003
Medical School (2nd yr), Cardiovascular Pharmacology Lectures, 2001-2003

Medical College of Wisconsin

Invited Lecturer, Graduate Pharmacology Course, "Mechanisms of Thrombolysis and Restenosis," October, 1991

University of California Santa Barbara

Invited Lecturer, Undergraduate Pharmacology Colloquia Series, "Fibrinogen Receptor Antagonists as Novel Therapeutics," February, 1992

University of Michigan Medical School

Graduate Level Cardiovascular Pharmacology, Medical School Pharmacology, 1993-1995

Western Michigan University

Graduate Thesis Committee, Department of Biological Sciences, 1994-1998

POST-DOCTORAL SCIENTISTS TRAINED

Robert J. Leadley, Ph.D., 1990-1992

Christopher F. Toombs, Ph.D., 1991-1994

Anjali Kumar, Ph.D., 1995 - 1997

EXTRAMURAL MEETINGS ORGANIZED

"Role of Adhesion Molecules in Cardiovascular Pharmacology," ASPET Colloquium, University of Michigan, Ann Arbor, Michigan, June 1994.

"Pharmacological Interventions in Thrombosis and Thrombolysis," ASPET Colloquium, University of Michigan, Ann Arbor, Michigan, June 1995.

"Functional Genomics," ASPET Colloquium, Boston, MA, June 2000.

"Functional Genomics and Proteomics in Drug Discovery and Development, ASPET Symposium, Orlando, FL, April, 2001.

"Protein Therapeutics", ASPET Symposium, New Orleans, LA, April 2002.

EXTRAMURAL INVITED PRESENTATIONS

"Thromboxane Receptor Antagonists and Myocardial Ischemia," organizer and speaker for minisymposium hosted by Philadelphia Physiological Society, Philadelphia, Pennsylvania, September, 1987.

"Thromboxane Receptor Antagonism vs. Thromboxane Synthase Inhibition in Prevention and Interruption of Thrombosis," invited seminar, Department of Pharmacology, Royal College of Surgeons, London, England, November, 1987.

"Role of Thromboxane A₂ in Thrombosis and Thrombolysis," invited seminar, Department of Cardiology, Thomas Jefferson University, Philadelphia, Pennsylvania, February, 1988.

"Thromboxane Receptor Antagonists as Adjunctive Agents to Thrombolytic Therapy," chairman and speaker for ASPET Symposium entitled, "Thromboxane Receptor Antagonists in Acute Myocardial Infarction," Montreal, Canada, October, 1988.

"Thromboxane Receptor Antagonism in Models of Thrombosis and Thrombolysis," invited seminar, Department of Pharmacology, Temple University, Philadelphia, Pennsylvania, January, 1989.

"Animal Models for Thrombosis/Thrombolysis Research," invited seminar, Department of Cardiology, University of Michigan, Ann Arbor, Michigan, September, 1990.

"Fibrinogen Receptor (GPIIb/IIIa) Antagonism," invited lecture, Cardiovascular Discussion Group, Princeton, New Jersey, October, 1990.

"Drug Discovery Targets in Thrombosis," invited lecture, Mid-Atlantic Pharmacology Society, Princeton, New Jersey, October, 1990.

"Fibrinogen Receptor Antagonism as Anti-thrombotic Therapy," symposium speaker, FASEB, Atlanta, Georgia, April, 1991.

"Novel Approaches to Prevention of Restenosis," invited seminar, Department of Pharmacology, Medical College of Wisconsin, Milwaukee, Wisconsin, October, 1991.

"Principles Underlying the Use of Conjunctive Agents with Plasminogen Activators," invited speaker, NYAS, Plasminogen Activation in Fibrinolysis in Tissue Remodeling and Development, Amsterdam, The Netherlands, October, 1991.

"Development of Fibrinogen Receptor Antagonists as Novel Antithrombotics," invited seminar, Department of Pharmacology, University of Michigan Medical School, Ann Arbor, Michigan, February, 1992.

"Development of Fibrinogen Receptor Antagonists as Novel Antithrombotics," invited seminar, Department of Biological Sciences, Western Michigan University, Kalamazoo, Michigan, April, 1992.

"Interruption of Thrombosis and Hemostasis by Anti-Platelet Agents," organizer and speaker in symposium entitled "Perturbation of Hemostasis Following Novel Anti-Platelet, Anticoagulant and Thrombolytic Therapy," Society of Toxicological Pathologists, Phoenix, Arizona, June, 1992.

"Interruption of Smooth Muscle Cell Proliferation Following Balloon Angioplasty in the Rat with the Novel 2 Aminochromone, U-86983," invited seminar, Department of Pharmacology, University of Michigan, Ann Arbor, Michigan, June, 1993.

"Interruption of Smooth Muscle Cell Proliferation Following Balloon Angioplasty in the Rat with the Novel 2 Aminochromone, U-86983," invited seminar, Department of Pharmacology, University of Minnesota, Minneapolis, Minnesota, July, 1993.

"Pharmacological Intervention in Thrombosis," organizer and speaker for ASPET mini-symposium, San Francisco, California, August, 1993.

"Development of Novel Agents for Prevention of Smooth Muscle Cell Proliferation and Restenosis Following Balloon Angioplasty," invited seminar, Physiology Department, Michigan State University, East Lansing, Michigan, September, 1993.

"Development of Novel Agents for Prevention of Smooth Muscle Cell Proliferation and Restenosis Following Balloon Angioplasty," invited seminar, Department of Pharmacology, Uniformed Services University, Bethesda, Maryland, October, 1993.

"Role of Adhesion Molecules in Thrombosis and Restenosis," invited seminar, F.E. Shideman Distinguished Alumnus Awardee Lecture, Department of Pharmacology, University of Minnesota, Minneapolis, Minnesota, April, 1994.

"Role of P-Selectin in Thrombosis and Restenosis," invited seminar, Department of Biological Sciences, Western Michigan University, Kalamazoo, Michigan, September, 1994.

"Role of P-Selectin in Thrombosis and Restenosis," invited seminar, Department of Pharmacology,

University of Michigan, Ann Arbor, Michigan, September, 1994.

"Adhesion Molecules in Cardiovascular Pharmacology," Bronson Methodist Hospital, Kalamazoo, Michigan, March, 1995.

"Adhesion Molecules in Cardiovascular Pharmacology," Borgess Hospital, Kalamazoo, Michigan, March, 1995.

"*In Vivo* Pharmacology of P-Selectin Antagonism," organizer, chair and speaker for ASPET Symposium, San Diego, California, March, 1997.

"Role of P-selectin in Thrombogenesis and Neointimal Proliferation Following Vascular Injury" invited speaker at IBC's 7th annual international conference on cell adhesion molecules and matrix proteins, August, 1997.

"Role of P-selectin in the Pathophysiology and Diagnosis of Acute Coronary Syndromes" invited seminar, Dept. of Pharmacology, University of Minnesota, November, 2000.

"Novel Application of Anti-Platelet GPIIb/IIIa Inhibitors; Prevention of Post-Surgical Adhesions", invited seminar, Dept. of Integrative Biology & Physiology, University of Minnesota, October, 2006.

"A Process for Identifying and Commercializing Novel Academic-Based Technology", invited speaker, Safety Pharmacology Society, Boston, MA, September 2010.

"Competitive Landscape in Anti-Platelets and Anti-Coagulants " invited speaker, SomaLogic, Inc., Boulder, CO, January 2011.

GRANT SUPPORT
Recently Completed

Title: Nitric Oxide releasing ultra-slippy antibacterial surfaces for urological catheter applications
Application Number: 1 R43 DK136411-01A1 (SBIR Phase I)
PI: Shebuski (Nytricx, Inc.) \$337,395
Supporting Agency: NIH/NIDDK
Period of Performance: 7/15/23-7/14/24

Funded (Ongoing)

Title: Achieving homeostasis in traumatic injuries with a nitric oxide-driven antimicrobial dressing combined with a rapid blood clotting agent
Application Number: DM220089 (DoD/USArmy)
PI: Shebuski (Nytricx, Inc.) \$1,114,225
Supporting Agency: DoD/CDMRP/USAMRDC
Period of Performance: 9/01/23-8/30/25

Title: Ultra-low Fouling and Anti-infective and Anti-thrombotic Nitric Oxide Releasing Intravascular Catheters
Application Number: 2 R42 HL149595-02A1 (STTR Phase II)
PI: Shebuski (Nytricx, Inc.) \$2,346,606
Supporting Agency: NIH/NHLBI
Period of Performance: 9/14/23-7/31/25

Title: Enhanced Prosthetic Vascular Graft Function by Local Release of Nitric Oxide (NO)
Application Number: 1R41HL176245-01 (STTR Phase I)
PI: Shebuski (Nytricx, Inc) and Garren (UGA) \$311,824
Supporting Agency: NIH/NHLBI
Period of Performance: 9/1/24-8/31/25

Title: Prevention of ECMO Circuit Thrombosis and Infection by Surface Release of Nitric Oxide (NO)
Application Number: 19-2024-0659-F
PI: Shebuski (Nytricx, Inc.) \$745,973
Supporting Agency: BARDA DRIVe Healing Lungs
Period of Performance: 9/9/24-3/9/26

PUBLICATIONS

Journal and Book Articles

1. Aiken, J.W., Gorman, R.R. and Shebuski, R.J. Prevention of blockage of partially obstructed coronary arteries with prostacyclin correlates with inhibition of platelet aggregation. *Prostaglandins* 17:483-494, 1979.
2. Aiken, J.W., Gorman, R.R. and Shebuski, R.J. Prostacyclin prevents blockage of partially obstructed coronary arteries. In: Prostacyclin (J. R. Vane and S. Bergstrom, eds.), Raven Press, New York, 1979, p. 311.
3. Miller, O.V., Aiken, J.W., Hemker, D.P., Shebuski, R.J. and Gorman, R.R. Prostacyclin stimulation of dog arterial cyclic AMP levels. *Prostaglandins* 18:915-929, 1979.
4. Aiken, J.W. and Shebuski, R.J. Comparison in anesthetized dogs of the anti-aggregatory and hemodynamic effects of prostacyclin and a chemically stable prostacyclin analog, 6a-carba-PGI₂ (carbacyclin). *Prostaglandins* 19:629-643, 1980.
5. Aiken, J.W., Shebuski, R.J. and Gorman, R.R. Blockage of partially obstructed coronary arteries with platelet thrombi: Comparison between cyclooxygenase inhibitors *versus* prostacyclin. In: Advances in Prostaglandin and Thromboxane Research (B. Samuelsson, P. Ramwell and R. Paoletti, eds.), Raven Press, New York, 1980, Vol. 7, p. 635.
6. Miller, O.V., Aiken, J.W., Shebuski, R.J. and Gorman, R.R. 6-Keto-prostaglandin E₁ is not equipotent to prostacyclin (PGI₂) as an antiaggregatory agent. *Prostaglandins* 20:391-400, 1980.
7. Gallagher, K.P., Folts, J.D., Shebuski, R.J., Rankin, J.H.G. and Rowe, G.G. Subepicardial vasodilatory reserve in the presence of critical coronary stenosis in dogs. *Amer. J. Cardiology* 46:67-73, 1980.
8. Gorman, R.R., Miller, O.V., Shebuski, R.J. and Aiken, J.W. Prostacyclin mediated inhibition of canine coronary artery obstruction by platelets: Correlation with platelet and arterial cyclic AMP levels. In: The Regulation of Coagulation (K. G. Mann and F. B. Taylor, eds.). Elsevier Publishing, North-Holland, 1980, Vol. 8, p. 439.
9. Hemker, D.P., Shebuski, R.J. and Aiken, J.W. Release of a prostacyclin-like substance into the circulation of dogs by intravenous adenosine 5'-diphosphate. *J. Pharmacol. Exp. Ther.* 212:246-252, 1980.
10. Shebuski, R.J. and Aiken, J.W. Angiotensin II stimulation of renal prostaglandin synthesis elevates circulating prostacyclin in the dog. *J. Cardiovasc. Pharmacol.* 2:667-677, 1980.
11. Shebuski, R.J. and Aiken, J.W. Angiotensin II induced renal prostacyclin release suppresses platelet aggregation in the anesthetized dog. In: Advances in Prostaglandin and Thromboxane Research (B. Samuelsson, P. Ramwell and R. Paoletti, eds.), Raven Press, New York, 1980, Vol. 7, p. 1149.

12. Aiken, J.W., Shebuski, R.J., Miller, O.V. and Gorman, R.R. Endogenous prostacyclin contributes to the efficacy of a thromboxane synthetase inhibitor for preventing coronary artery thrombosis. *J. Pharmacol. Exp. Ther.* 219:299-308, 1981.
13. Gorman, R.R., Shebuski, R.J., Aiken, J.W. and Bundy, G.L. Analysis of the biological activity of azoprostanoids in human platelets. *Fed. Proc.* 40:19-22, 1981.
14. Taylor, B.M., Shebuski, R.J. and Sun, F.F. Circulating prostacyclin metabolites in the dog. *J. Pharmacol. Exp. Ther.* 224:691-698, 1983.
15. Zollikofer, C.L., Casteneda-Zuniga, W., Einzig, S., Cragg, A., Ryshavy, J., Bruhlmann, W.F., Shebuski, R.J. and Amplatz, K. The role of prostaglandins in percutaneous transluminal angioplasty. *Radiology* 149(3):681-685, 1983.
16. Zeigler, D.W., Shebuski, R.J. and Zimmerman, B.G. Central and peripheral cardiovascular action of urapidil in normotensive and Goldblatt hypertensive animals. *Amer. J. Med.* 77(4A):81-86, 1984.
17. Shebuski, R.J. and Zimmerman, B.G. Suppression of reflex tachycardia following alpha adrenoceptor blockade in conscious dogs: Comparison of urapidil to prazosin. *J. Cardiovasc. Pharmacol.* 6:788-794, 1984.
18. Shebuski, R.J. and Zimmerman, B.G. Comparison of urapidil with the alpha₂-adrenoceptor agonists, clonidine and B-HT 920, on responses of transmurally stimulated guinea pig ileum. *Proc. Soc. Exp. Biol. and Med.* 178:133-138, 1985.
19. Shebuski, R.J. and Zimmerman, B.G. Suppression of reflex tachycardia by central administration of the alpha₁-adrenoceptor antagonists, urapidil and prazosin, in anesthetized dogs. *J. Pharmacol. Exp. Ther.* 234:456-462, 1985.
20. Shebuski, R.J., Fujita, T., Smith, J.M., Jr., Kopaciewicz, L., Blumberg, A.L. and Hieble, J.P. Suppression of sympathetic ganglionic neurotransmission by the selective dopamine-1 agonist, fenoldopam (SK&F 82526), in the anesthetized dog. *J. Pharmacol. Exp. Ther.* 235:735-740, 1985.
21. Rassier, M.E., Shebuski, R.J. and Zimmerman, B.G. Beta₁-adrenoceptor antagonism by urapidil prior to and after treatment with the selective alpha₂-adrenoceptor antagonist, rauwolscine in anesthetized dogs. *Eur. J. Pharmacol.* 122:37-43, 1986.
22. Shebuski, R.J., Fujita, T. and Ruffolo, R.R. Jr. Evaluation of alpha₁- and alpha₂-adrenoceptor-mediated vasoconstriction in the *in situ*, autoperfused pulmonary circulation of the anesthetized dog. *J. Pharmacol. Exp. Ther.* 238:217-222, 1986.
23. Shebuski, R.J., Fujita, T. and Ruffolo, R.R., Jr. Interaction of dopamine (+)-dobutamine and the (-)-enantiomer of dobutamine with alpha- and beta- adrenoceptors in the pulmonary circulation of the dog. *Pharmacology*, 34:201-212, 1987.

24. Shebuski, R.J., Fujita, T., Smith, J.M., Jr. and Ruffolo, R.R., Jr. Comparison of the alpha-adrenoceptor activity of dopamine, ibopamine and epinine in the pulmonary circulation of the dog. *J. Pharmacol. Exp. Ther.*, 241:6-12, 1987.
25. Shebuski, R.J., Ohlstein, E.H., Smith, J.M., Jr. and Ruffolo, R.R., Jr. Enhanced pulmonary alpha₂-adrenoceptor responsiveness under conditions of elevated pulmonary vascular tone. *J. Pharmacol. Exp. Ther.* 242:158-165, 1987.
26. Ohlstein, E.H., Storer, B., Fujita, T. and Shebuski, R.J. Streptokinase and tissue-type plasminogen activator (t-PA) induce platelet hyperaggregability in the rabbit. *Throm. Res.* 46:575-585, 1987.
27. Nichols, A., Smith, J.M., Jr., Shebuski, R.J. and Ruffolo, R.R., Jr. Comparison of the effects of ibopamine, epinine, dopamine and fenoldopam on vascular dopamine receptors in the anesthetized dog. *J. Pharmacol. Exp. Ther.* 242:573-578, 1987.
28. Nichols, A. J., Shebuski, R.J. and Ruffolo, R.R., Jr. Inhibition of plasma cholinesterase prevents the dopamine DA-1 receptor mediated renal vasodilation produced by ibopamine. *Eur. J. Pharmacol.* 141:515-518, 1987.
29. Shebuski, R.J., Smith, J.M., Jr. and Ruffolo, R.R., Jr. Comparison of the renal and pulmonary effects of fenoldopam, dopamine, dobutamine and norepinephrine in the anesthetized dog. *Pharmacology* 36:35-43, 1988.
30. Shebuski, R.J., Smith, J.M., Storer, B.L., Granett, J.R. and Bugelski, P.R. Influence of the selective thromboxane A₂/endoperoxide receptor antagonist sulotroban on lysis time and reocclusion rate following tPA-induced coronary thrombolysis. *J. Pharmacol. Exp. Ther.* 246:790-796, 1988.
31. Shebuski, R.J., Storer, B.L. and Fujita, T. Effect of thromboxane synthase inhibition on the thrombolytic action of tissue-type plasminogen activator (tPA) in a rabbit model of peripheral arterial thrombosis. *Throm. Res.* 52:381-392, 1988.
32. Hieble, J.P., Kopia, G.A., Shebuski, R.J. and Ruffolo, R.R. The role of postjunctional alpha₂-adrenoceptors in the control of vascular resistance, In: Vascular Neuroeffector Mechanisms: Receptors, Ion Channels, Second Messengers and Endogenous Mediators. (Bevan, J.A., Majewski, H., Maxwell, R.A. and Story, D.F., eds),. IRL Press, Oxford, 1988, pp. 49-56.
33. Connors, R.W., Sweet, R.W., Noveral, J., Pfavr, D., Trill, T., Shebuski, R.J., Berkowitz, B.A., Williams, D., Franklin, S. and Reff, M. DHFR Coamplification of tPA in DHFR Positive Bovine Endothelial Cells: *In vitro* characterization of the purified serine protease. *DNA*, 7:651-661, 1989.
34. Ohlstein, E.H., Horohonich, S., Shebuski, R.J. and Ruffolo, R.R., Jr. Localization and characterization of the canine pulmonary alpha₂-adrenoceptor. *J. Pharmacol. Exp. Ther.*, 248:233-239, 1989.

35. Shebuski, R.J., Bloom, J.C., Sellers, T.S., Fujita, T., Storer, B., Horohonich, S., Fong, K.L. and Ohlstein, E.H.: Attenuation of the inhibitory effect of prostacyclin on platelet function after tissue plasminogen activator or streptokinase infusion in the rabbit. *Fibrinolysis*, 3:115-123, 1989.
36. Shebuski, R.J., Smith, J.M., Jr. and Ruffolo, R.R., Jr. Effects of dopamine, ibopamine and epinine on alpha- and beta- adrenoceptors in the pulmonary circulation of the dog. *Fund. Clin. Pharmacol.*, 3:211-221, 1989.
37. Shebuski, R.J., Berry, D., Bennett, D., Romoff, T., Storer, B.L., Ali, F. and Samanen, J. Demonstration of Ac-Arg-Gly-Asp-Ser-NH₂ as an antiaggregatory agent in the dog by intracoronary administration. *Throm. Haemo.*, 61:183-188, 1989.
38. Kopia, G.A., Kopaciewicz, L.J., Ohlstein, E.H., Horohonich, S., Storer, B.L. and Shebuski, R.J. Combination of the thromboxane receptor antagonist, sulotroban (BM 13.177, SK&F 95587), with streptokinase: Demonstration of thrombolytic synergy. *J. Pharmacol. Exp. Ther.* 250:877-895, 1989.
39. Fujita, T., Hasan, S., Storer, B.L. and Shebuski, R.J. Effect of selective endoperoxide/thromboxane A₂ receptor antagonism with sulotroban on tPA-induced thrombolysis in a rabbit model of femoral arterial thrombosis. *Fund. Clin. Pharmacol.* 3:643-653, 1989.
40. Shebuski, R.J., Ramjit, D.R., Bencen, G.H. and Polokoff, M.A. Characterization and platelet inhibitory activity of bitistatin, a potent RGD-containing peptide from the venom of the viper, *Bitis arietans*. *J. Biol. Chem.* 264:21550-21556, 1989.
41. Shebuski, R.J., Sitko, G.R., Claremon, D.A., Baldwin, J.J., Remy, D.C. and Stern, A.M. Acceleration of tPA-induced thrombolysis by inhibition of factor XIIIa in a canine model of coronary arterial thrombosis. *Blood*, 75:1455-1459, 1990.
42. Shebuski, R.J., Stabilito, I.J., Sitko, G.R. and Polokoff, M.H. Acceleration of tPA-induced thrombolysis by the RGD-containing peptide bitistatin, and prevention of reocclusion by the combination of heparin and bitistatin in a canine model of coronary thrombosis. *Circulation*, 82:169-177, 1990.
43. Shebuski, R.J., Ramjit, D.R., Lumma, P.K. and Garsky, V.M. Prevention of canine coronary artery thrombosis with echistatin, a potent inhibitor of platelet aggregation from the venom of the viper *Echis carinatus*. *Thromb. Haemo.*, 64:576-581, 1990.
44. Bush, L.R. and Shebuski, R.J. *In vivo* models of arterial thrombosis and thrombolysis: *FASEB Journal*, 4:3087-3098, 1990.
45. Mayer, E.J., Fujita, T., Gardell, S.J., Shebuski, R.J. and Reilly, C.F. The pharmacokinetics of plasminogen activator inhibitor-1 in the rabbit. *Blood*, 76:1514-1520, 1990.

46. Trill, J.J., Fong, K.L., Shebuski, R.J., McDevitt, P., Johanson, K., Williams, D., Boyle, K.E., Sellers, T.S. and Reff, M.E. Expression and characterization of finger protease (FP): a mutant tissue-type plasminogen activator (t-PA) with improved pharmacokinetics. *Fibrinolysis*, 4:131-140, 1990.
47. Reilly, C.F., Mayer, E.J., Hutzelmann, J.E., Sitko, G.R., Gardell, S.J. and Shebuski, R.J. The effect of exogenous plasminogen activator inhibitor-1 in a canine model of occlusive thrombus formation. *Fibrinolysis*, 5:99-104, 1991.
48. Reilly, C.F., Fujita, T. and Shebuski, R.J. Plasminogen activator inhibitor-1 inhibits endogenous fibrinolysis in a canine model of pulmonary embolism. *Circulation*, 84:287-292, 1991.
49. Vlasuk, G.P., Ramjit, D., Dunwiddie, C.T., Nutt, E.M., Fujita, T., Smith, D.E. and Shebuski, R.J. Comparison of the *in vivo* anticoagulant properties of standard heparin and the highly specific factor Xa inhibitors antistasin and tick anticoagulant peptide (TAP) in a rabbit model of venous thrombosis. *Thromb. Haemo.*, 65:257-262, 1991.
50. Gardell, S.J., Ramjit, D.R., Stabilito, I.I., Fujita, T., Lynch, J.J., Cuca, G.C., Deepak, J., Wang, S., Tung, J., Mark, G.E. and Shebuski, R.J. Effective thrombolysis without marked plasminemia following bolus intravenous administration of a vampire bat salivary plasminogen activator in rabbits. *Circulation*, 84:244-253, 1991.
51. Holohan, M.A., Mellott, M.J., Garsky, V.M. and Shebuski, R.J. Prevention of reocclusion following tPA-induced thrombolysis by the RGD-containing peptide, echistatin, in a canine model of coronary thrombosis. *Pharmacology*, 42:340-348, 1991.
52. Shebuski, R.J. Emerging drug discovery targets in thrombosis and coagulation. *Ann. Rep. Med. Chem.*, 26:93-101, 1991.
53. Shebuski, R.J. Principles underlying the use of conjunctive agents with plasminogen activators. *N.Y. Acad. Sci.* 667:382-394, 1992.
54. Toombs, C.F., Norman, N.R., Groppi, V.E., Lee, K.S., Gadwood, R.C., and Shebuski, R.J. Limitation of myocardial injury with the potassium channel opener cromakalim and the non-vasoactive analog U-89,232: Vascular versus cardiac actions in vitro and in vivo. *J. Pharmacol. Exp. Ther.* 263:1261-1268, 1992.
55. Benjamin, C.W., Lin, A.H., Morris, J., Wishka, D.M., Gammill, R.B., Shebuski, R.J. and Gorman, R.R. Inhibition of human platelet aggregation by novel 2-animochromone phospholipase C inhibitors. *Developments in Oncology*, 71: (Eicosanoids Other Bioact. Lipids in Cancer. *Inflammation Radiat. Inj.*) 231-3, ISSN: 0167-4927, 1993.
56. Hartman, J.C., Hullinger, T.G., Wall, T.M., and Shebuski, R.J. Reduction of myocardial infarct size by ramiprilat is independent of angiotensin II synthesis inhibition. *Eur. J. Pharmacol.* 234:229-236, 1993.

57. Hartman, J.C., Wall, T.M., Hullinger, T.G., and Shebuski, R.J. Reduction of myocardial infarct size in rabbits by ramiprilat: Reversal by the bradykinin antagonist, HOE 140. *J. Cardiovas. Pharmacol.* 21:996-1003, 1993.
58. Morris, J., Wishka, D.G., Lin, A.H., Humphrey, W.R., Wiltse, A.L., Gammill, R.B., Judge, T.M., Bisaha, S.N., Bergh, C.L., Cudahy, M.M., Thomas, E.W., Gorman, R.R., Benjamin, C.W., and Shebuski, R.J. Synthesis and biological evaluation of antiplatelet 2-aminochromones. *J. Med. Chem.* 36:2026-2032, 1993.
59. Shebuski, R.J. Pharmacology of anti-platelet agents. *Thrombosis and Haemorrhage*, Blackwell Scientific Publications, (Ed: Loscalzo and Schafer), pp. 1139-1154, 1993.
60. Leadley Jr., R.J., Lee, P., Erickson, L.A., Shebuski, R.J. The snake venom peptide Sarafotoxin S6b inhibits repetitive platelet thrombus formation in the stenosed canine coronary artery. *J. Cardiovas. Pharmacol. Supplement.* 22(Suppl.8):S199-203, 1993.
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