

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

UNITED THERAPEUTICS CORPORATION,
Petitioner,

v.

ACTELION PHARMACEUTICALS LTD,
Patent Owner.

IPR2025-01139

**DECLARATION OF DR. LUKE HOWARD IN SUPPORT OF PATENT
OWNER'S PRELIMINARY RESPONSE**

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DECLARATION OF DR. LUKE HOWARD

I, Luke Howard, DPhil MB BChir FRCP, 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, Luke Howard, DPhil MB BChir FRCP, have been retained as an expert by Sidley Austin LLP on behalf of Actelion Pharmaceuticals Ltd (Actelion) to provide an analysis of issues concerning the validity of U.S. Patent No. 8,268,847 (the '847 patent).

2. I have been informed that United Therapeutics Corporation (UT) has challenged the validity of the '847 patent by filing a petition for *inter partes* review (IPR) before the U.S. Patent Trial and Appeal Board. From reading UT's Petition, I understand that UT asserts three grounds of unpatentability against claims 1-57 of the '847 patent: Ground 1 (Anticipation by Bolli); Ground 2 (Obviousness over Bolli in view of Keyser); and Ground 3 (Obviousness over Bolli, Hoeper, and Morice).

3. I have been asked to review and evaluate UT's Petition and the expert declaration of Dr. Ronald J. Shebuski, Ph.D. (EX1013) submitted by UT. This declaration sets out my initial opinions in response to the issues raised by UT and Dr. Shebuski.

4. I am being compensated for my work on this matter at my standard rate of GBP £750 per hour. No part of my compensation depends on the content of my opinions rendered or the outcome of these proceedings.

5. I am an expert in the field of cardiopulmonary medicine, including the diagnosis and treatment of patients with cardiopulmonary conditions including pulmonary arterial hypertension (PAH), as well as clinical investigation into new and emerging therapies to treat such diseases.

6. I currently serve as the Director at the National Pulmonary Hypertension Service at Hammersmith Hospital, Imperial College Healthcare NHS Trust. I am also a Professor of Practice in Cardiopulmonary Medicine, at the National Heart & Lung Institute, Imperial College London. I have worked as a Consultant Pulmonologist at this institution since 2006.

7. I obtained a Doctor of Philosophy (DPhil) in Physiological Sciences from the University of Oxford in 1994 and a medical degree (MB BChir) from the University of Cambridge in 1996. In 1999, I completed my professional exams in General (Internal) Medicine to be admitted as a Member of the Royal College of Physicians in London, UK. I was admitted as a Fellow in 2010.

8. As part of my role as a researcher, I have served on steering committees as an investigator for clinical studies investigating treatments for PAH conducted by various sponsors, including Actelion, Apollo Therapeutics, Bristol-

Myers Squibb, Gossamer Bio, and SoniVie. In particular, I have been a steering committee member or investigator for clinical trials concerning endothelin receptor antagonists such as macitentan, as well as other therapies to treat PAH.

9. In my work on these various steering committees and as a chief investigator designing clinical trials, I collaborate extensively with teams that include other physicians, clinical pharmacologists, and other medical professionals.

10. As a clinician-researcher, I have been a driving and integral part of a multicentre network gaining grant funding for studying both novel compounds and repurposing others in the field of PAH. In this network, I have collaborated closely with basic and translational scientists, clinician scientists, cardiologists, pulmonologists, and clinical, experimental and non-clinical pharmacologists. I have been a scientific advisor to ATXA Therapeutics since 2020, which is developing a novel drug for the treatment of PAH.

11. I have authored or co-authored over 200 original scientific manuscripts, the majority in the field of PAH and other cardiopulmonary diseases. I have also been involved in numerous symposia and the development of guidelines for the treatment of PAH and other cardiopulmonary diseases since at least 2008.

12. Further information about my education, academic background, publications, and practice experience can found in my curriculum vitae, which is attached to this declaration as Appendix A.

II. Materials Considered

13. The opinions in this declaration are mine. They are based on my analysis in this matter, informed by the knowledge, education, experience, training, and skill I have accumulated in the course of my career of more than 25 years as a medical doctor, clinician, and researcher of cardiopulmonary medicine.

In addition to drawing from my own experience, my opinions are based on review of UT's Petition and accompanying exhibits (including the expert declaration of Dr. Ronald J. Shebuski, Ph.D. (EX1013)) as well as the following documents:

Exhibit#	Reference Name
2017	Revatio [®] Label
2018	Adcirca [®] Label
2019	Jacobs, M., <i>Mechanism of Action of Hydralzaine on Vascular Smooth Muscle</i> , BIOCHEM. PHARMACOL. 33(18): 2915-2919 (1984)
2020	Nielsen-Kudsk, J.E. et al., <i>K⁺ channel opening: a new drug principle in cardiovascular medicine</i> , 76 HEART 109-116 (1996)
2021	Packer, M. et al., <i>Double-Blind, Placebo-Controlled Study of the Efficacy of Flosequinan in Patients With Chronic Heart Failure</i> , JACC 22(1): 65-72 (July 1993)
2022	Resnick, M.S. et al., <i>Flosequinan, a vasodilator with a novel mechanism of action</i> , 102 BR. J. PHARMACOL. 974 (1991)
2023	Stassi, D.L. et al., <i>Ethyl-substituted erythromycin derivatives produced by directed metabolic engineering</i> , 95 PROC. NATL. ACAD. SCI. USA 7305 (1998)

Exhibit#	Reference Name
2024	Humbert, M. et al., <i>Treatment of Pulmonary Arterial Hypertension</i> , N. ENGL. J. MED. 351(14): 1425-1436 (Sept 2004)
2025	Schneider, M.P. et al., <i>Contrasting Actions of Endothelin ET_A and ET_B Receptors in Cardiovascular Disease</i> , 47 ANNU. REV. PHARMACOL. TOXICOL. 731 (2007)
2026	Lee, S.H. & Channick, R.N., <i>Endothelin Antagonism in Pulmonary Arterial Hypertension</i> , SEMINARS IN RESPIRATORY & CRITICAL CARE MED. 26(4): 402-408 (2005)
2027	Rubin, L.J. et al., <i>Bosentan Therapy for Pulmonary Arterial Hypertension</i> , N. ENGL. J. MED. 346(12): 896-903 (Mar. 2002)
2028	Humbert, M. et al., <i>Combination of bosentan with epoprostenol in pulmonary arterial hypertension: BREATHE-2</i> , 24 EUR. RESPIR. J., 353 (2004)
2029	McLaughlin, V. et al., <i>Randomized study of adding inhaled iloprost to existing bosentan in pulmonary arterial hypertension</i> , 174 AM. J. RESPIR. CRIT. CARE MED. 1257-63 (2006)
2030	Hooper, M. et al., <i>Combining inhaled iloprost with bosentan in patients with idiopathic pulmonary arterial hypertension</i> , 28 EUR. RESPIR. J., 691 (2006)
2031	Sica, D.A. & Gehr, T.W.B., <i>Direct Vasodilators and their Role in Hypertension Management: Minoxidil</i> , J. CLIN. HYPERTENSION III(II): 110-114 (Mar./Apr. 2001)
2032	Paul, G.A., <i>Bosentan decreases the plasma concentration of sildenafil when coprescribed in pulmonary hypertension</i> , 60 BR. J. CLIN. PHARMACOL. 107-112 (2005)

III. Legal Principles I Have Been Asked To Apply

14. I am not a lawyer, and I have not been asked to offer legal opinions.

As a scientific expert, I understand that my analysis involves presenting scientific information and applying certain legal principles.

A. Person of Ordinary Skill in the Art (POSA)

15. I have been informed that I am to perform my analysis from the perspective of a person of ordinary skill in the art (POSA) as of the priority date of

the '847 patent. I have been told to assume that the priority date is August 29, 2006. I understand that a POSA is a hypothetical individual with skills and experience relevant to the technology at issue who is presumed to know all the relevant prior art. I understand that a POSA is one with ordinary creativity, and is neither a genius nor an automaton.

16. The '847 patent focuses on macitentan in combination with compounds having PDE5-inhibitory properties for therapeutic use in the treatment of diseases involving vasoconstriction. For purposes of the '847 patent, it is my opinion that a POSA would be a clinician, specifically a pulmonologist or cardiologist, with an M.D. or comparable medical degree, with at least 3-5 years of experience in diagnosing and treating diseases involving vasoconstriction, such as *e.g.*, PAH. The clinician would also likely be part of a larger team that would include basic, translational, and clinical scientists in the field of pharmacology, cell biology, animal models, and clinical trials, who study drug therapy candidates.

17. In August 2006, I would have met and exceeded my own definition of a POSA. Where required, and as instructed by counsel, I have conducted my analysis through the eyes of a POSA.

18. Dr. Shebuski has opined in his declaration that a 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.” EX1013, ¶ 22.

19. Dr. Shebuski’s definition of a POSA requires a degree and experience in pharmacology, but does not require any specific clinical experience in treating diseases involving vasoconstriction. My definition of a POSA requires such clinical experience. Furthermore, the POSA I described above would be knowledgeable about commercially available treatment options for diseases involving vasoconstriction, and assessing potential combination drug products to treat such diseases. A POSA would also have an understanding of preclinical experimentation, and *in vitro* or animal models used in exploring potential treatments in PAH. While a POSA would have knowledge of these preclinical studies, they would not necessarily be conducting these studies themselves. A POSA would be capable of understanding the results from the necessary experiments, which practically would be conducted by a pharmacologist or preclinical scientist in the course of developing a drug.

B. Anticipation

20. I understand that claims of a patent are anticipated (and therefore invalidated) if a single prior art reference discloses each and every element of the claim, and that the prior art disclosure is arranged just as in the claim (rather than

multiple distinct teachings that a POSA might somehow combine to achieve the claimed invention). For a prior art reference to anticipate, I understand there must be no difference between the claimed invention and the reference's disclosure, as viewed by a POSA.

21. I also understand that there is no anticipation if the single reference is missing a limitation. To the extent every limitation is not found in an asserted reference, I understand it is legal error to look to secondary sources outside of the asserted reference to attempt to fill in those missing limitations in an anticipation analysis.

C. Obviousness

22. I understand that a claimed invention in a patent may be invalid even if each element of the claim is not found in a single prior art reference, if the claimed invention would have been obvious to a POSA as of the patent's priority date based on the prior art as a whole.

23. I have been informed that obviousness should be evaluated based on the scope and content of the prior art and the differences between the prior art and the claimed invention, while taking into account the level of ordinary skill in the art. I understand that when assessing whether a given claim is obvious, I am to compare the asserted prior art reference(s) against the claim, and consider whether

such differences would have been obvious to a POSA as of the priority date of the patent.

24. I understand that the obviousness inquiry should not be done in hindsight. That is, the analysis should avoid considering what is known today, what was learned from the '847 patent's teachings, and using the '847 patent as a roadmap for selecting and combining prior art references.

25. I understand that in order for a claimed invention to be proven obvious based on elements independently known in the prior art, there must be a showing of some motivation for a POSA to combine the prior art references and a reasonable expectation of success in doing so. I also understand that for an obviousness analysis, each of the elements of the claims must still be met by the combination of prior art references.

26. I have also been informed that teachings in the prior art may, in some cases, dissuade or discourage a POSA from making the claimed invention or lead a POSA in a different direction from practicing the claimed invention. I understand that such evidence of the prior art teaching away from the claimed invention should be considered and tends to show that the claimed invention is not obvious.

27. I understand that objective indicia of non-obviousness should also be considered when evaluating whether a claimed invention would have been obvious to a POSA at the time of invention. I understand that these objective indicia may

include, for example, unexpected results achieved by the invention, praise of the invention by others skilled in the art, a long-felt but unmet need in the prior art that was satisfied by the claimed invention, deliberate copying of the invention, or commercial success of products covered by the patent.

D. Claim Construction

28. I understand that the words of a claim are generally given their ordinary and customary meaning as understood by a POSA as of the priority date when read in the context of the patent specification and prosecution history. I have been informed that there are two exceptions to this general rule: (1) when the patentee acts as a “lexicographer” and sets out his or her own definition of a term in the patent specification; or (2) when the patentee disavows the full scope of a claim term either in the specification or during prosecution of the patent.

29. For purposes of this declaration, I have applied the definitions for claim terms as they are set forth in the '847 patent. For any remaining terms, I have used the plain and ordinary meaning as would be understood by a POSA at the time of invention. I have not been asked, at this time, to take any positions with respect to claim constructions proposed by UT or its expert Dr. Shebuski. I reserve the right to submit further opinions regarding claim construction should that become necessary in these proceedings.

IV. Relevant Scientific Background

A. The Circulatory System

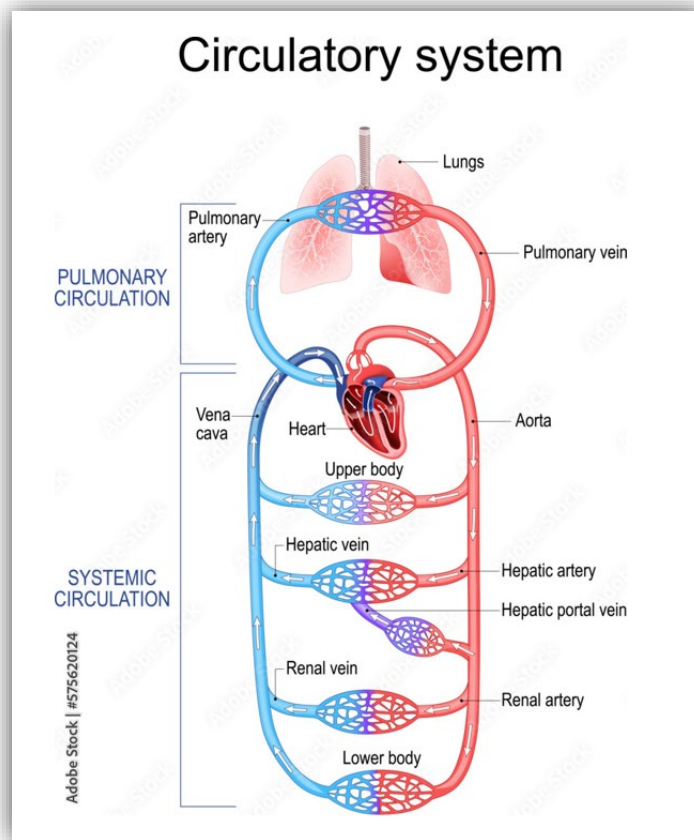
30. There are two circulatory systems which control the circulation of blood between the lungs, the heart, and the rest of the body: the systemic and pulmonary circulatory systems. Both systems consist of a network of organs and blood vessels, *e.g.*, arteries, veins, and capillaries.

31. The *systemic circulatory system* is responsible for delivering oxygenated blood from the left ventricle of the heart to organs and tissues in the body, then returning deoxygenated blood from those organs and tissues back to the right atrium of the heart.

32. The *pulmonary circulatory system* is responsible for delivering deoxygenated blood from the right ventricle of the heart to the lungs, then returning oxygenated blood from the lungs back to the left atrium of the heart, for subsequent circulation to the rest of the body.

33. The diagram below illustrates the pulmonary circulatory system and systemic circulatory system.¹

¹ Retrieved from: [Adobe Stock Images, File #: 575620124](#).



B. Overview of Pulmonary Arterial Hypertension

34. In healthy patients, the blood pressure of the pulmonary circulatory system is very low. For example, while normal blood pressure in the systemic circulatory system is 120/80 mmHg, normal blood pressure in the pulmonary circulatory system is between 14 ± 3 mmHg. This low pulmonary blood pressure is maintained through the exchange of oxygen through the thin walls of the lungs and the pulmonary blood vessels.

35. PAH is a serious condition that affects the pulmonary circulatory system. At a high level, this condition is caused by the narrowing or tightening of

blood vessels, known as vasoconstriction, which increases blood pressure in the pulmonary circulatory system to an abnormally high level. Patients with PAH typically have a pulmonary blood pressure of 21 mmHg or higher.

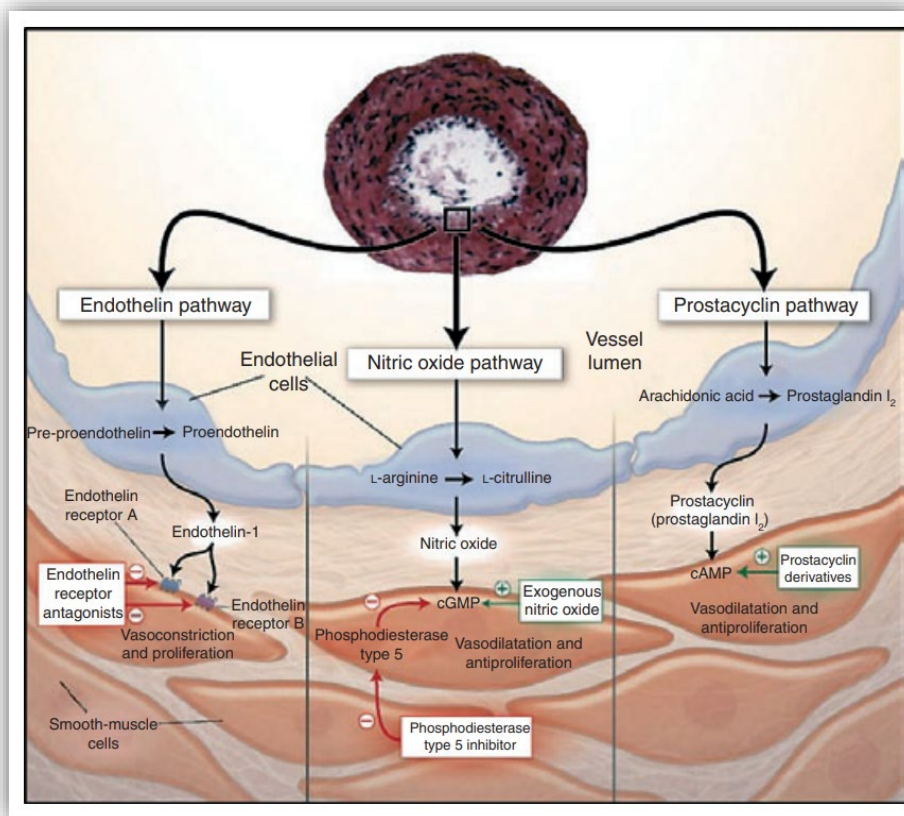
36. PAH is a disease marked by increased blood pressure in the pulmonary arteries. Specifically, the arterial walls of the lungs constrict and thicken, thereby increasing resistance to blood flow and causing the right ventricle of the heart to work harder to pump blood through the narrowed arteries to the lungs. This causes extra stress and hypertrophy (enlargement) of the right ventricle, which in turn causes the right ventricle to weaken over time, ultimately leading to heart failure in patients.

37. PAH is a progressive and incurable disease that is difficult to detect in its early stages since the symptoms of PAH are nonspecific and gradual. As a result, even by the time PAH is diagnosed and a patient is started on treatment, the disease may have already progressed significantly.

C. Treatment of PAH

38. PAH can be treated by disrupting various processes in the body that cause blood vessels to constrict. In 2006, the three major biological pathways that were known to mediate vasoconstriction and remodelling (thickening of the vessel wall and narrowing of vessel lumen) were: (1) the endothelin pathway, (2) the nitric oxide (NO) pathway, and (3) the prostacyclin pathway. These pathways are

illustrated in the diagram below. EX2024, 1427. Two of these pathways, the endothelin and NO pathways, are relevant here.



1. The Endothelin Pathway and Endothelin Receptor Antagonists

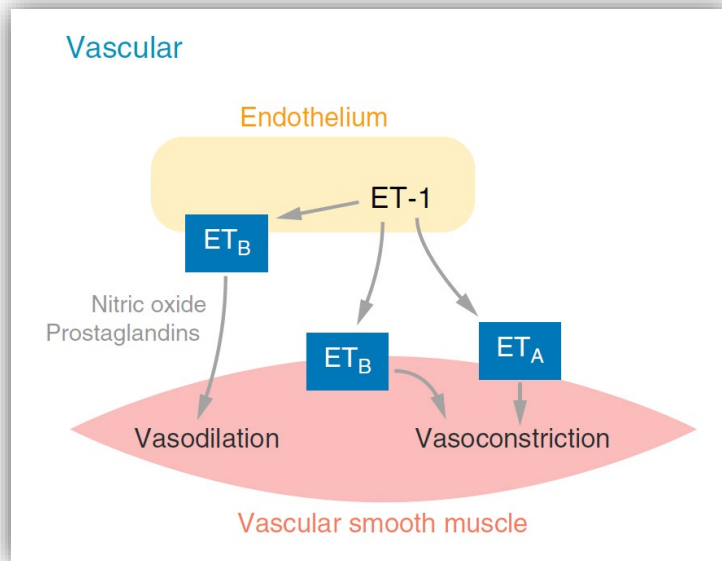
39. The cells lining blood vessels are called endothelial cells, and they release a peptide called endothelin. Endothelin is a potent vasoconstrictor, meaning it induces vasoconstriction. There are three endothelin isoforms, or variants, which are encoded by separate genes and differ in their amino acid sequence: ET-1, ET-2, and ET-3. ET-1 is the most important isoform in the pulmonary circulatory system.

40. In healthy patients, circulating ET-1 levels are low. Patients with PAH, however, have elevated ET-1 levels, both circulating and more importantly within the vessel wall, which results in increased vasoconstriction and increased blood pressure in the pulmonary arteries.

41. ET-1 acts on endothelin receptors, which, depending on the receptor subtype, causes different downstream effects. ET-1 mediates vasoconstriction/vasodilation upon binding to two endothelin receptor types: ET_A and ET_B. The ET_A receptor is found on vascular smooth muscles, which is the muscle tissue within the walls of pulmonary blood vessels. The binding of ET-1 to the ET_A receptor causes vasoconstriction, which increases pulmonary blood pressure. The binding of ET-1 to the ET_A receptor also has vasoproliferative effects, meaning it causes abnormal growth and remodelling of vascular cells, which further increases pulmonary blood pressure.

42. In contrast, the ET_B receptor has multiple functions, depending on its location. Binding of ET-1 to the ET_B receptor located on endothelial cells mediates the clearance of ET-1 in circulation, and causes vasodilation through stimulating the release of nitric oxide and prostacyclin. Both of these functions reduce pulmonary blood pressure. However, binding of ET-1 to ET_B located on the smooth muscle layer causes vasoconstrictive and vasoproliferative effects, similar to ET_A receptors.

43. The diagram below illustrates the receptor-specific functions of endothelin that influence vasoconstriction and vasodilation. EX2025, 733.



44. Endothelin receptor antagonists (ERAs) bind and inhibit one or both of ET_A and ET_B, which blocks the activity of ET-1, thereby inhibiting ET-1's vasoconstrictive effect. Through this antagonistic action, ERAs can cause vasodilation in the pulmonary circulatory system, which reduces pulmonary blood pressure.

45. As of August 2006, only one ERA was approved in the U.S. for the treatment of PAH: bosentan (Tracleer®). Bosentan was the first oral therapy for treatment of PAH. Another ERA, sitaxsentan, was approved in Europe in 2006, but was never approved by the U.S. FDA, and was withdrawn worldwide due to a risk of fatal liver damage. Other ERAs were known and in clinical development in

2006. For example, ambrisentan was in development and later approved in 2007 in the U.S. as Letairis[®].

46. Bosentan is a dual, or nonselective ERA, meaning it targets both ET_A and ET_B receptors. EX2026, 403. In comparison, sitaxsentan and ambrisentan selectively target ET_A receptors, and are thus called “selective ET_A receptor antagonists.”² *Id.*, 405-406.

47. Another ERA developed by Actelion is macitentan. Like bosentan, macitentan is a dual antagonist. EX1011, 6; EX1024, 6-7; *see also* § IV.D, below.

48. In the early- to mid-2000s, many scientists were studying ERAs. In particular, special attention was paid to ERAs that selectively bind to ET_A because the mechanism of the ET_A receptor was better understood and has more direct vasoconstrictive effects, whereas the ET_B receptor has both vasoconstrictive and vasodilatory effects. For example, while dual antagonists block vasoconstriction from ET_A receptors, they could also interfere with the beneficial actions of ET_B receptors, including ET-1 clearance and ET_B-stimulated vasodilation. *See, e.g.*, EX1005, 20-21 (“ET_A causes vasoconstriction, while ET_B causes vasodilatation. Bosentan works by blocking both ET_A and ET_B receptors. Sitaxsentan works by

² In this declaration, I will refer to selective ET_A receptor antagonists as “ETA-selective antagonists.”

only blocking the ET_A and leaving the ET_B unimpaired. . . . Nonselective antagonists would not function as effectively because they block the ET_B stimulated cGMP production.”); EX2026, 405 (“Given the opposing actions of ET_A and ET_B, it may be advantageous to selectively antagonize the ET_A receptor while allowing the ET_B receptor to remain unopposed. This has the theoretical advantage of blocking the deleterious vasoconstrictive and vascular smooth muscle proliferative effects mediated through ET_A while maintaining the beneficial vasodilatory and ET-1 clearance actions of ET_B”).

2. The Nitric Oxide (NO) Pathway and PDE5 Inhibitors

49. In the nitric oxide (NO) pathway, endothelial cells produce NO, which acts as a potent pulmonary vasodilator. When the smooth muscle cells are exposed to this NO, the production of a molecule called cyclic guanosine monophosphate (cGMP) is stimulated. cGMP is a potent vasodilator that relaxes the vascular smooth muscle. Certain enzymes, most predominantly phosphodiesterase type 5 (PDE5), naturally break down cGMP in the pulmonary circulatory system.

50. In patients with PAH, NO levels are reduced and PDE5 levels in the pulmonary vasculature are increased, which results in reduced cGMP. This limits vasodilation in the pulmonary arteries, which leads to increased vasoconstriction and increased pulmonary blood pressure.

51. PDE5 inhibitors target the NO pathway by reducing PDE5 activity, thereby preventing the breakdown of cGMP. This increases cGMP, resulting in increased vasodilation and reduced pulmonary blood pressure.

52. In 2006, there were a few PDE5 inhibitors in clinical development, but the only one approved for treatment of PAH in the U.S. was sildenafil (Revatio[®]) (approved in 2005). *See, e.g.*, EX2017. In 2009, FDA approved use of another PDE5 inhibitor, tadalafil (Adcirca[®]), for treatment of PAH. *See, e.g.*, EX2018.

53. The endothelin pathway and NO pathway are closely related, because the mechanism through which ET_B causes vasodilation is through stimulation of NO, which leads to increased cGMP. Therefore, cGMP production may be stimulated through activating both the endothelin *and* NO pathways.

3. Combination Therapies

54. As of August 2006, clinical trials conducted in patients with PAH demonstrated the safety and efficacy of treatments studied as monotherapy. For example, the clinical trials investigating sildenafil (the SUPER study published in 2005) and bosentan (the BREATHE-I study published in 2002) investigated the effects of these treatments as compared to placebo in PAH patients. *See, e.g.*, EX1041, 1; EX2027, 896-897.

55. As of August 2006, there was some interest in seeing whether approved PAH treatments could be combined for the treatment of PAH, because patients on medication for PAH had progressively worsening symptoms, but there was a lack of evidence or guidance regarding which drugs were best to combine, let alone the timing of treatments, and the dosage amounts to limit possible side effects of any potential combination therapy.

56. Importantly, the clinical evidence demonstrating the effects of combination therapies was in its infancy. For example, the BREATHE-2 study, published in 2004, investigated the combination of bosentan and epoprostenol in 33 patients but failed to meet its clinical endpoint. EX2028, 357-358. Two open-label studies testing the combination of bosentan with iloprost had opposite results. The STEP study, published in 2006, demonstrated that the combination therapy was well tolerated in the small group of patients tested, with a signal towards efficacy. EX2029, 1257. On the other hand, the COMBI study, also published in 2006, was stopped due to futility. EX2030, 691.

D. Overview of Macitentan

57. Macitentan was developed by Actelion as a treatment for PAH. It was approved for sale in the U.S. in 2013 under the trade name OPSUMIT®. The '847 patent covers, among other things, a combination therapy developed by Actelion for the treatment of PAH: administration of macitentan and the PDE5 inhibitor

tadalafil. This combination product was approved for sale in the U.S. in 2024 under the trade name OPSYNVI®.

58. Macitentan is a dual ET_A/ET_B antagonist, as demonstrated through both *in vitro* and *in vivo* tests. The properties of macitentan were reported in publications by Iglarz et al. (2008), and Bolli et al. (2012).

59. From Iglarz, it was reported that macitentan is a “dual ET_A/ET_B endothelin (ET) receptor antagonist” which exhibits “inhibitory potency on both ET receptors” and “antagonize[s] the specific binding of ET-1 on membranes of cells overexpressing ET_A and ET_B receptors.” EX1011, 2. Three *in vitro* assays demonstrated macitentan’s dual antagonism: (1) a receptor binding assay testing the binding affinity and inhibitory potency of macitentan to the ET_A and ET_B receptors; (2) a functional assay testing the level of inhibition of ET-1 induced contraction by macitentan in rat aortic and tracheal tissue; and (3) a panel of radioligand assays to test the selectivity of macitentan for ET_A and ET_B receptors compared to other receptors in the body. *Id.*, 6.

60. In a binding assay, the IC₅₀ (half-maximal inhibitory concentration) is the concentration of a compound that is required to displace 50% of a known ligand from its target. The IC₅₀ value is a measure of a compound’s potency in that specific assay but it is not an intrinsic measure of the compound’s binding affinity. While a ratio of IC₅₀ values (often called a “selectivity ratio”) is often used as a

convenient estimate of selectivity, its accuracy depends heavily on the binding model and assay conditions.

61. From Iglarz's *in vitro* receptor binding assays, macitentan inhibited binding of ET-1 to ET_A with an IC₅₀ value of 0.50 ± 0.2 nM, and inhibited binding of ET-1 to ET_B with an IC₅₀ value of 391 ± 182 nM. A selectivity ratio can be calculated by dividing the IC₅₀ value for ET_B by the IC₅₀ value for ET_A. Thus, according to Iglarz based on this assay, macitentan's selectivity ratio based on IC₅₀ values is 782. EX1011, 6. The same results were reported in Bolli 2012. EX1024, 6-7.

62. Iglarz's *in vitro* functional assays revealed that macitentan inhibited ET-1 induced contraction in isolated rat tissue. Two types of tissue were tested: (1) rat aortic tissue with the ET_A receptor, and (2) rat tracheal tissue with the ET_B receptor. From these assays, the pA₂ values, which are a measure of potency of a competitive antagonist, of macitentan on ET_A and ET_B tissue were compared and macitentan demonstrated an ET_A / ET_B inhibitory potency ratio of 50:1. EX1011, 6.

63. To further assess its selectivity *in vitro*, macitentan was screened at a high concentration (10 µM) in a panel of 63 radioligand binding assays. Such radioligand binding assays are used to show whether a compound selectively inhibits certain receptors by showing that it does not inhibit binding of other

receptors in the body. Through this screening, Iglarz et al. found that “macitentan did not inhibit by more than 50% the binding of any of the ligands tested,” showing that “macitentan is selective for the ET_A and ET_B receptors.” EX1011, 6.

64. Taken together, the three *in vitro* assays in Iglarz (and additionally in Bolli 2012) show that macitentan is a dual antagonist. Additionally, Iglarz reported:

Macitentan is best studied *in vivo* because this allows the study of the overall pharmacological effects of macitentan together with its metabolite. The dual ET_A/ET_B receptor antagonism of macitentan was tested in rats by measuring plasma ET-1 concentrations. When administered to normotensive rats, ***macitentan, like bosentan, increased plasma ET-1 concentration, confirming its dual blockade on both ET_A and ET_B receptors.*** This increase occurred at a 10-fold lower dose than with bosentan, indicating a more potent pharmacological activity *in vivo* (Fig. 2).

EX1011, 6.

65. The *in vivo* results reported in Iglarz confirm what the *in vitro* results showed, which is that macitentan is a dual antagonist.

66. Throughout Dr. Shebuski’s declaration, he states that a POSA would have understood that macitentan is a “selective ET_A antagonist.” *See, e.g.,* EX1013, ¶¶ 187, 285, 370, 374. However, I disagree with Dr. Shebuski’s and UT’s characterization of macitentan as an ET_A-selective antagonist because it is unsubstantiated and inaccurate based on what has been reported about macitentan, as discussed above. Because macitentan was demonstrated to bind both the ET_A

and ET_B receptors and exhibit potent inhibitory effects on both receptors, it should be (and is) considered a dual, or nonselective, ERA.

V. The '847 Patent Inventions

67. The '847 patent is titled “Therapeutic Compositions Comprising A Specific Endothelin Receptor Antagonist and a PDE5 Inhibitor.” I understand that the application leading to the '847 patent was filed August 28, 2007, and that the patent issued on September 18, 2012. The patent issued in 2012 had 11 claims. I understand that the patent was subject to a supplemental examination by the USPTO, after which a reexamination certificate issued on April 16, 2018, which includes 46 additional claims, for a total of 57 claims.

68. As discussed above, I have been informed that the “priority date” of the patent is August 29, 2006, and that UT has not challenged this priority date.

69. The '847 patent discusses the use of a “compound of formula (I)” — which is the ERA now known as macitentan—in combination with “at least one compound having PDE5-inhibitory properties” for the “treatment of a disease wherein vasoconstriction is involved.” EX1001, Abstract.

70. The '847 patent description includes a series of definitions, including what is intended by a “compound having PDE-5 inhibitory properties,” and provides examples of specific PDE5 inhibitors that were known at the time, including sildenafil, vardenafil, tadalafil and udenafil. EX1001, 1:45-59; 2:39-42.

71. The patent further explains that diseases involving vasoconstriction may include hypertension, pulmonary hypertension (PH), PAH, diabetic arteriopathy, heart failure, erectile dysfunction or angina pectoris. EX1001, 2:35-38. Amongst these diseases, a POSA would be familiar with ERAs and PDE5 inhibitors and their role in treating PAH, and would understand that a primary focus of the '847 patent is the use of macitentan in combination with PDE5 inhibitors to treat PAH.

72. The '847 patent has three examples that report the effects of the combination of macitentan and PDE5 inhibitors in two different rat models, the Dahl salt-sensitive (Dahl-S) rat and spontaneously hypertensive rat (SHR) models. EX1001, 5:13-6:9. In each of these examples, macitentan and a PDE5 inhibitor (either sildenafil or tadalafil) were administrated separately and then in combination, and the effects of the separate and combined therapies on the rats' blood pressure were measured. *Id.*, 5:13-6:50. The treatment effect of each therapy (or their combination) was measured by measuring the area beneath the curve (ABC) of two curves: the blood pressure of the control period (before administration of the therapy) and blood pressure of the treatment period. *Id.*, 5:65-6:3. The ABCs represent a change in blood pressure, so it is a way to measure whether blood pressure was decreased in the subject.

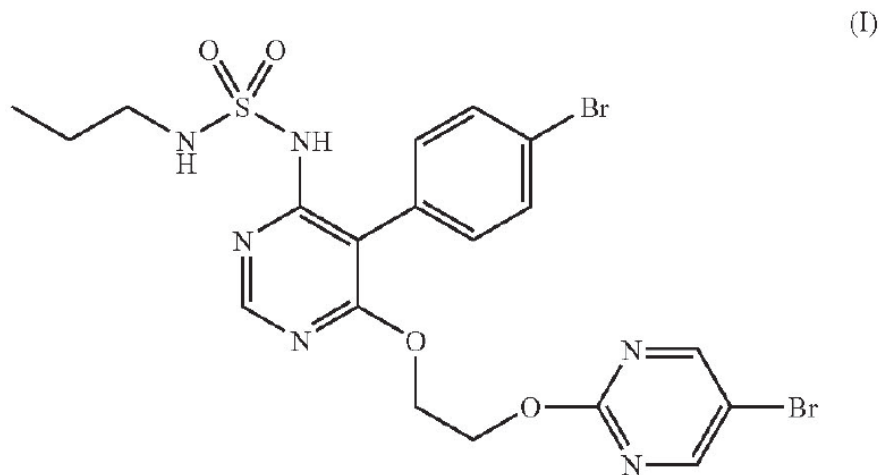
73. Examples 1-3 of the '847 patent show that macitentan and the PDE5 inhibitor resulted in a decrease in blood pressure in the rat models and, when administered together, the effect was greater than the sum of the compounds' effects when administered alone. EX1001, 6:51-7:19. The table below summarizes the ABCs calculated in each experiment:

Experiment	Macitentan (0.3 mg/kg)	Tadalafil (10 mg/kg)	Macitentan (0.3 mg/kg) & Tadalafil (10 mg/kg)
Dahl-S (Example 1)	256	310	923
SHR (Example 2)	44	286	444
	Macitentan (0.3 mg/kg)	Sildenafil (30 mg/kg)	Macitentan (0.3 mg/kg) & Sildenafil (30 mg/kg)
SHR (Example 2)	38	229	317

74. These experiments each describe the combination of macitentan and PDE5 inhibitors as demonstrating a synergistic effect in reduction of blood pressure in hypertension rat models. A POSA would conclude from these results that administering macitentan in combination with a PDE5 inhibitor would result in a synergistic effect in the treatment of hypertension, and that these results could be translated specifically to the treatment of PH and PAH.

75. The '847 patent has 57 claims. Independent claim 1 recites:

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



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

EX1001, cl. 1.

76. There are two additional independent claims. Independent claim 6 recites a pharmaceutical composition with macitentan and at least one PDE5 inhibitor. Independent claim 10 recites a method of treatment for hypertension or PH comprising administering macitentan in combination with at least one PDE5 inhibitor.

77. Claims 2-5, 7-9, and 11-57 depend from one of claims 1, 6, or 10 and set forth additional limitations including specific PDE5 inhibitors, specific diseases involving vasoconstriction, methods of administration, and dosages.

78. Unless otherwise specified, and only for the purposes of this declaration in support of Actelion's Preliminary Response, my analysis is primarily focused on the limitations recited in claim 1, which include two limitations that are required by all claims: a compound of formula (I) (macitentan) in combination with at least one compound having PDE5-inhibitory properties. I reserve the right to address additional limitations and additional issues in the future if necessary.

VI. Response to UT's Challenges

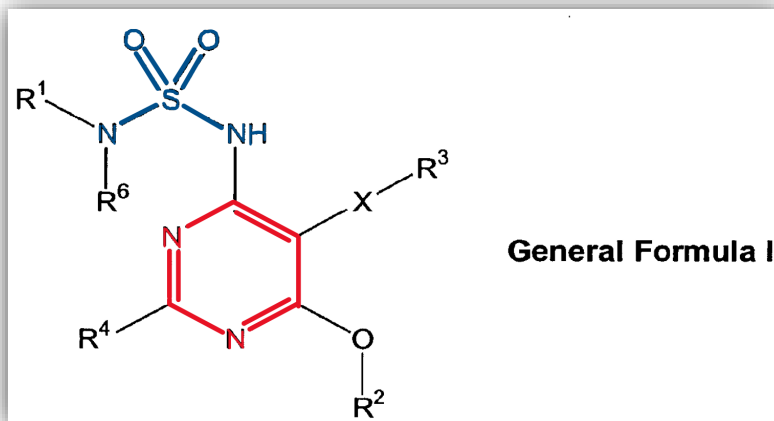
A. Prior Art Relied Upon by UT

1. Bolli (EX1004)

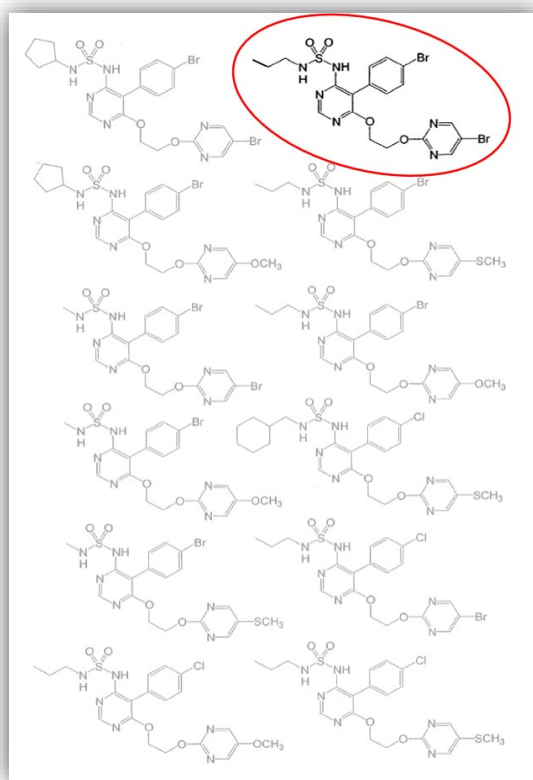
79. Bolli is an international patent application filed by Actelion titled "Novel Sulfamides And Their Use As Endothelin Receptor Antagonists." EX1004, 1. I understand Bolli was published on July 11, 2002. *Id.*

80. Bolli generally describes "pyrimidine-sulfamides of the general formula I and their use as active ingredients in the preparation of pharmaceutical compositions." EX1004, 2. The class of compounds of general formula I described in Bolli all share the same core structure, which includes a pyrimidine (red in the annotated figure below) and sulfamide group (blue). In addition to the core structure, the compounds in Bolli have up to six additional chemical groups or structures, indicated by X, R¹ through R⁴ and R⁶ in the figure below. *Id.*, 13-16. Bolli provides various options for each of the X and R groups, which may result in

the formation of virtually hundreds or thousands of potential compounds. *Id.*, 13-14.



81. Bolli identifies a group of “preferred compounds” of Formula I as well as additional “preferred compounds” of Formulae II-V, which vary in these X and R groups. EX1004, 19-24. After identifying compounds of “Formula V,” Bolli discloses “[a]nother group of preferred compounds,” consisting of 60 compounds, all depicted by skeletal structure without names. *Id.*, 25-29. Macitentan is one of these compounds. Below is a reproduction of the page in Bolli that depicts macitentan, with macitentan circled in red:



Id., 29.

82. Other than where the chemical structure is shown, macitentan is not mentioned or discussed elsewhere in Bolli. Though macitentan appears amongst a group of 60 compounds that are described as “another group of preferred compounds,” there are several groups of “preferred compounds” and “especially preferred compounds” of general Formula I described throughout Bolli. EX1004, 19-29. Thus, there are likely hundreds of “preferred compounds” discussed in Bolli, including the 60 that are shown by structure. Bolli does not state or suggest a preference for macitentan in particular.

83. Bolli also describes chemical reactions that may be used to prepare compounds of general formula I, and provides exemplary compounds of general formula I made through these reactions. EX1004, 5, 30-37, 66-111. These compounds are labeled Examples 1 through 214. There are some gaps in the numbering, but it appears Examples 1-214 contain about 185 compounds. I have been informed that only 3 of these 185 compounds overlap with the 60 compounds previously discussed. *Id.*, 96 (Examples 117 and 118), 110 (Example 197). As a whole, Bolli therefore provides the structures of close to 250 exemplary compounds, though it likely describes more.

84. Bolli further discusses compounds of general formula I and “their use as endothelin receptor antagonists,” and reports the ET_A- and ET_B-selective binding profiles of some of the Examples 1-214. EX1004, 4-9. Though Bolli provides the IC₅₀ values for some of the Examples 1-214, and states that “compounds exhibiting mixed as well as ET_A-selective binding profiles have been identified,” it does not indicate which compounds exhibit “mixed” binding profiles and which compounds exhibit “ET_A-selective” binding profiles. *Id.*, 3-9.

85. Macitentan does not appear in the list of Examples 1-214 and Bolli does not report anything about the specific binding profile of macitentan. A POSA would not understand Bolli to be providing data about the specific selectivity or potency of macitentan. Therefore, a POSA could not read Bolli to substantiate any

of Dr. Shebuski's claims that macitentan was known to be selective for ET_A over ET_B. *See, e.g.*, EX1013, ¶¶ 187, 285, 370, 374.

86. Dr. Shebuski also opines in his declaration that the selectivity and potency of macitentan, though not disclosed in Bolli, can be estimated by comparison to Example 104, which Dr. Shebuski contends is the most similar to macitentan. EX1013, ¶¶ 44, 360. However, a POSA would not necessarily look to Example 104 as providing any relevant information about macitentan. First, Example 104 is not identical to macitentan. Second, Bolli does not contain any teaching or suggestion that Example 104 would exhibit the same selectivity or potency as macitentan. Third, a POSA would not have any reason to believe that a similar, but not the same, chemical structure would behave the same way. For example, generic therapeutics must include the same active ingredient as a reference compound to be approved by regulatory agencies.

87. In one sentence, Bolli teaches that the compounds of general formula I can be used in combination with a variety of other therapeutic agents, including:

- *α- and β-blockers* like phentolamine, phenoxybenzamine, atenolol, propranolol, timolol, metoprolol, carteolol and the like;
- *vasodilators* like hydralazine, minoxidil, diazoxide or flosequinan;
- *calcium-antagonists* like diltiazem, nicardipine, nimodipine, verapamil or nifedipine;

- *ACE-inhibitors* like cilazapril, captopril, enalapril, lisinopril and the like;
- *potassium activators* like pinacidil;
- *angiotensin II receptor antagonists* like losartan, valsartan, irbesartan and the like;
- *diuretics* like hydrochlorothiazide, chlorothiazide, acetolamide, bumetanide, furosemide, metolazone or chlortalidone;
- *sympatholitics* like methyl dopa, clonidine, guanabenz or reserpine;
- and *other therapeutics* which serve to treat high blood pressure or any cardiac disorders.

EX1004, 18 (emphases added).

88. Notably, Bolli does not mention PDE5 inhibitors, or the combination of compounds of general formula I with PDE5 inhibitors.

2. Keyser (EX1005)

89. Keyser is an international patent application titled “Endothelin A receptor (ET_A) Antagonists In Combination With Phosphodiesterase 5 Inhibitors (PDE5) and Uses Thereof.” EX1005, 1. I understand Keyser was published on March 9, 2006. *Id.*

90. Keyser describes “combination therapies comprising an endothelin A receptor (ET_A) antagonist and a phosphodiesterase 5 (PDE5) inhibitor” and

methods of treating various disorders by “administering an ET_A antagonist and a PDE5 inhibitor.” EX1005, 2.

91. Keyser discusses multiple therapies to treat systemic hypertension and PAH , including diuretics, sympathetic-nerve blockers (such as beta blockers), and vasodilators (such as hydralazine, minoxidil, and diazoxide), as well as PDE5 inhibitors and ERAs. EX1005, 3-7. Keyser also discusses drawbacks of these therapies in treating PAH. *Id.*, 20. For example, PDE5 inhibitors like sildenafil “have several adverse effects,” and require high doses to achieve a therapeutic effect against PAH. *Id.*, 11, 20. For that reason, Keyser explains that “it would be beneficial to combine a PDE5 inhibitor with an ET_A antagonist to provide complimentary treatment and reduce dosage amounts and/or side effects related to treatment with PDE5 inhibitors.” *Id.*, 11.

92. Keyser goes on to explain its recommendation for combining an ET_A antagonist with a PDE5 inhibitor. Keyser explains that “use of a nonselective ET receptor interferes with multiple pathways whereas use of a specific ET_A antagonist will act in a complementary fashion for the multiple pathways” which in turn “provide[s] superior efficacy and/or dosage regimes and/or reduction in side effects.” EX1005, 20.

93. Keyser explains:

ET_A causes vasoconstriction, while ET_B causes vasodilatation.
Bosentan works by blocking both ET_A and ET_B receptors.

Sitaxsentan works by only blocking the ET_A and leaving the ET_B unimpaired. The mechanism by which ET_B causes vasodilatation is through stimulating the production of nitrous oxide and prostacylin. Nitrous oxide (NO) in turn activates the guanyl cyclase which increases the level of cGMP. The cGMP is responsible for relaxing the blood vessel. PDE5 acts to break down cGMP, so a PDE5 inhibitor also raises the level of cGMP, causing vasodilatation. Thus, when used together, increasing cGMP through the ET_A receptor and preventing its breakdown leads to increased vasodilatation and better efficacy of both drugs. ***Nonselective antagonists would not function as effectively because they block the ET_B stimulated cGMP production.*** Additionally in a recent study, Bosentan, a non-selective antagonist, was tested with sildenafil, but the study was terminated due to pharmacokinetic drug interaction problems.

EX1005, 20-21 (emphases added)

94. A POSA would understand Keyser to be identifying a problem with nonselective ET_A/ET_B antagonists, which is that they interfere with multiple pathways and in particular, do not function as effectively in combination with PDE5 inhibitors because they block ET_B-stimulated cGMP production. Keyser offers the solution to that problem, which is to use an ET_A-selective antagonist in combination with a PDE5 inhibitor like sildenafil. Keyser explains that when used together, the combination of an ET_A-selective antagonist and a PDE5 inhibitor can increase the level of cGMP *and* prevent its breakdown, thereby increasing the vasodilative effect. EX1005, 21.

95. By way of example, Keyser mentions bosentan, the only approved endothelin receptor at the time of Keyser's publication. Keyser explains that bosentan is a "nonselective compound that blocks both the A and the B receptors."

EX1005, 20. Keyser highlights that bosentan “was tested with sildenafil, but the study was terminated due to pharmacokinetic drug interaction problems.”

EX1005, 21. Given these perceived drawbacks of bosentan, Keyser focuses instead on sitaxsentan, which is an ET_A-selective antagonist. Keyser’s examples focus on sitaxsentan in combination with sildenafil. EX1005, 28-30.

96. Keyser does not disclose macitentan. Moreover, since Keyser’s focus is entirely on the use of *ET_A antagonists* with PDE5 inhibitors, a POSA would not read Keyser to be recommending or suggesting the use of a dual or nonselective antagonist, like macitentan, in combination with PDE5 inhibitors.

3. Hoeper (EX1009, EX1047)

97. Hoeper is a report titled “Combination therapy with bosentan and sildenafil in idiopathic pulmonary arterial hypertension” by M.M. Hoeper et al.. Hoeper reports on a study following nine patients with severe idiopathic PAH (IPAH) who were being treated with bosentan and experienced “transient clinical improvement, eventually followed by a decline in exercise tolerance.” EX1009, 1. These nine patients received adjunct treatment with sildenafil, in addition to already-prescribed bosentan. *Id.*, 1.

98. The efficacy of the treatments was measured through the 6-min walk distance (6MWD) and cardiopulmonary exercise testing (CPET). The 6MWD test measures the distance a patient can walk in 6 minutes on a flat surface. It is a

common test used by physicians to assess exercise capacity and impairment of cardiorespiratory functions. CPET is another diagnostic test which evaluates the function of the heart and lungs during exercise. The patient is asked to perform exercise on a treadmill or bike, while heart monitors or other sensors track physiological parameters such as oxygen consumption, heart rate, blood pressure, etc.

99. Hoeper provides an “observational report” showing the effects of the combination of bosentan and sildenafil on patients’ 6MWD. EX1009, 2-3. Initially, the 6MWD at baseline was 346 ± 66 m and it improved to 403 ± 80 m after 3 months of using only bosentan. *Id.*, 3. Hoeper reports that this effect was not sustained, and after about 11 months, the 6MWD reduced to 277 ± 80 m, which was lower than baseline. *Id.* Then, sildenafil was added to bosentan, and 3 months later, the 6MWD increased to 392 ± 61 m (slightly above baseline) and the patients remained stable for next 6-12 months. *Id.* The CPET results revealed that oxygen uptake was increased in patients who took bosentan and sildenafil. *Id.*

100. The authors conclude that “combining bosentan and sildenafil *might* be feasible in patients with IPAH.” EX1009, 3. However, the authors note that the study also has “several inherent limitations,” including lack of control group, small patient population, and limited observation period. *Id.*

4. Morice (EX1010, EX1048)

101. Morice is a short report titled “Combination therapy with bosentan and phosphodiesterase-5 inhibitor in pulmonary arterial hypertension.” It is a response to the Hoeper article, and reports the experience of with a combination of bosentan and tadalafil in one 42-year-old male patient with IPAH. EX1010, 1.

102. Morice reports that prior combination treatment of bosentan and sildenafil resulted in a decrease in pulmonary artery systolic pressure (to 50 mmHg), as well as a doubling in exercise tolerance. EX1010, 1. However, the patient raised issues with compliance with the therapy, meaning that the patient admitted they were not able to follow the treatment plan with the prescribed therapy. *Id.* Therefore, tadalafil was substituted for sildenafil. Morice reports that the patient had a positive experience with tadalafil in combination with bosentan (citing a reduction in estimated pulmonary artery pressure to 61 mmHg), but does not otherwise provide any data. *Id.*

B. The '847 Patent Claims Are Not Anticipated By Bolli

103. I have been asked to consider the '847 patent and the Bolli reference to determine whether the claims are anticipated by Bolli. Based on my review and comparison of the claims of the '847 patent to Bolli, it is my opinion that the claims are not anticipated by Bolli because Bolli does not disclose each and every element of the claims. Specifically, all claims require a “compound having PDE5

inhibitory properties” and Bolli does not disclose PDE5 inhibitors. For at least this reason, it is my opinion that Bolli does not anticipate any of the claims of the ’847 patent.

104. Dr. Shebuski contends that a POSA would have understood Bolli to disclose PDE5 inhibitors through the use of the word “vasodilators” in one paragraph within Bolli. EX1013, ¶¶ 91-99. I disagree—a POSA would not have read Bolli to disclose PDE5 inhibitors due merely to its mention of “vasodilators.”

105. There are at least two main reasons why a POSA would not have understood Bolli’s disclosure of vasodilators to include PDE5 inhibitors. First, as discussed below, each of the exemplary vasodilators listed in Bolli has a mechanism of action that is separate and distinct from PDE5 inhibition, which was well-known at the time. Second, and most important, Bolli’s exclusion of known vasodilators as well as Bolli’s listing of drugs that have the effect of vasodilation but are identified as *different* drug categories suggests that Bolli’s vasodilators is meant to be narrowly read to only include the small group of vasodilators that are specifically listed.

106. As I summarized above, Bolli discloses hundreds of compounds of general formula I, and states that the compounds can be combined with various other classes of drugs. ¶¶ 80-83, 87. Specifically, Bolli states:

The compounds of general formula I may also be used in combination with one or more other therapeutically useful substances e.g. α - and β -blockers like phentolamine, phenoxybenzamine, atenolol, propranolol, timolol, metoprolol, carteolol and the like; vasodilators like hydralazine, minoxidil, diazoxide or flosequinan; calcium-antagonists like diltiazem, nicardipine, nimodipine, verapamil or nifedipine; ACE-inhibitors like cilazapril, captopril, enalapril, lisinopril and the like; potassium activators like pinacidil; angiotensin II receptor antagonists like losartan, valsartan, irbesartan and the like; diuretics like hydrochlorothiazide, chlorothiazide, acetolamide, bumetanide, furosemide, metolazone or chlortalidone; sympatholytics like methyldopa, clonidine, guanabenz or reserpine and other therapeutics which serve to treat high blood pressure or any cardiac disorders.

EX1004, 18 (emphases added).

107. Thus, Bolli teaches that the compounds of general formula I can be combined with one or more of eight classes of drugs including:

- α - and β -blockers;
- vasodilators;
- calcium-antagonists;
- ACE-inhibitors;
- potassium activators;
- angiotensin II receptor antagonists;
- diuretics; and
- sympatholytics.

108. Each of the classes of drugs listed above is named to reflect the mechanism of action of the drug. For example, alpha and beta blockers block either the alpha receptors located on the smooth muscles of blood vessels, or the beta receptors found in the heart or smooth muscle that are activated by certain hormones. Calcium antagonists, as the name suggests, block or inhibit the movement of calcium ions into cells. ACE inhibitors bind angiotensin-converting enzyme (ACE) which converts angiotensin I to angiotensin II, an endogenous vasoconstrictor. Angiotensin II receptors block angiotensin II from binding to its receptor. Potassium activators work by opening up potassium channels in cell membranes. Diuretics help treat fluid retention in patients with PAH. Sympatholytics inhibit the sympathetic nervous system.

109. Each of the drugs identified in Bolli as a “vasodilator”—hydralazine, minoxidil, diazoxide or flosequinan—are what a POSA would understand to be *direct* vasodilators, which are drugs that act directly on the smooth muscle to cause vasodilation. *See, e.g.*, EX2031, 110 (discussing “direct vasodilator drugs” including minoxidil and hydralazine). These drugs were all known to act directly on vascular smooth muscles in blood vessels to promote vasodilation by acting on cell surface receptors and ion channels (*i.e.*, through inhibiting calcium release that causes vasoconstriction (hydralazine), opening and activation of potassium channels (minoxidil and diazoxide), interfering with the inositol-

triphosphate/protein kinase C pathway (a key mechanism for vasoconstriction) and decreasing intracellular calcium (flosequinan)). EX2019, 2918; EX2020, 111; EX2021, 65; EX2022, 974.

110. By contrast, PDE5 inhibitors do not act directly on the smooth muscle cells in blood vessels, unlike those in the “vasodilators” class in Bolli. Instead, PDE5 inhibitors *indirectly* cause vasodilation through acting on the NO pathway. Specifically, as discussed in § IV.C.2 above, nitric oxide activates the production of cGMP, a potent vasodilator, and PDE5 inhibitors prevent the breakdown of cGMP caused by PDE5. Therefore, PDE5 inhibitors act as potentiators of the NO pathway.

111. Thus, each of the exemplary vasodilators listed in Bolli has a mechanism of action that is separate and distinct from PDE5 inhibition, and a POSA would not have interpreted “vasodilators” in Bolli to mean PDE5 inhibitors.

112. Due to their distinct mechanism of action, PDE5 inhibitors should have been listed in their own category *in addition to* the categories discussed above, had they been intended to be included. Dr. Shebuski’s reading of “vasodilators” is impermissibly broad and does not make sense in light of Bolli subcategorizing drugs according to their mechanism of action. For example, a POSA may have understood that drugs colloquially known as vasodilators could theoretically include all types of medications that relax and widen the blood

vessels, *i.e.*, cause vasodilation. However, under that understanding, a POSA would have expected “vasodilators” to include not only the exemplary vasodilators listed by Bolli (hydralazine, minoxidil, diazoxide or flosequinan), *but also* nitrates (not mentioned in Bolli), together with ACE inhibitors, calcium channel blockers, and alpha blockers, and potassium activators (which are all listed as separate categories in Bolli).

113. Given that some of the known drugs that have vasodilatory effects were either not listed in Bolli (e.g., nitrates), or are listed as *separate* classes of drugs (e.g., ACE inhibitors, calcium channel blockers, alpha blockers, and potassium activators), a POSA would interpret Bolli to be categorizing drugs based on their mechanism of action, as opposed to their ultimate effects. Therefore, a POSA would interpret Bolli’s “vasodilators” to have a narrower meaning, which does *not* include all drugs that have a vasodilatory effect. Specifically, a POSA would have interpreted Bolli’s “vasodilators” to be *direct* vasodilators, as discussed above.

114. For example, one class of drugs that is not mentioned in Bolli’s list that I discuss above is nitrate medications. Nitrates target the NO pathway to cause vasodilation by acting as NO donors. As a class, they are key drugs in the treatment of angina and systemic hypertension. Nitrates were also considered to be

closely-related to PDE5 inhibitors. In the absence of nitrates in Bolli, a POSA would certainly not read Bolli to include PDE5 inhibitors.

115. A POSA's reading of Bolli's "vasodilators" as not including PDE5 inhibitors is similar to what is disclosed in other prior art, including UT's asserted reference Keyser. Keyser discusses therapies that were used to treat severe hypertension, including "drugs called vasodilators, which dilate the arteries" and provides as examples three of the same drugs mentioned in Bolli: hydralazine, minoxidil and diazoxide. EX1005, 3-4 ("Oral vasodilators, which include hydralazine and minoxidil, are often used Treatment includes the intravenous administration of vasodilators such as diazoxide."). Keyser then separately discusses PDE5 inhibitors at length as a separate, different class of drugs. *Id.*, 5. Keyser explains, as I have above, that PDE5 inhibitors "promote[] the vasodilating effects of endogenous nitric oxide." EX1005, 5. Keyser thus considers PDE5 inhibitors separately from "vasodilators."

116. I also disagree with Dr. Shebuski's opinion that Bolli's disclosure of erectile dysfunction (ED) would have caused a POSA to think of PDE5 inhibitors like sildenafil (Viagra) and tadalafil (Cialis), which are both treatments for ED, in the context of a different paragraph mentioning "vasodilators." EX1013, ¶¶ 96-97.

117. Bolli mentions ED as one of 30 conditions that can be treated using the compounds of general formula I. Bolli states:

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, coronary diseases, cardiac insufficiency, renal and myocardial ischemia, renal failure, cerebral ischemia, dementia, migraine, subarachnoidal hemorrhage, Raynaud's syndrome and portal hypertension. They can also be used in the treatment or prevention of atherosclerosis, restenosis after balloon or stent angioplasty, inflammation, stomach and duodenal ulcer, cancer, prostatic hypertrophy, ***erectile dysfunction***, hearing loss, amaurosis, chronic bronchitis, asthma, gram negative septicemia, shock, sickle cell anemia, glomerulonephritis, renal colic, glaucoma, therapy and prophylaxis of diabetic complications, complications of vascular or cardiac surgery or after organ transplantation, complications of cyclosporin treatment, pain, hyperlipidemia as well as other diseases, presently known to be related to endothelin.

EX1004, 12 (emphasis added); *see also id.*, 17 (same list).

118. A POSA would not have read the mention of ED in this paragraph on page 12 of Bolli to have any bearing on what Bolli meant by “vasodilators” on page 18. The paragraph mentioning ED does not mention vasodilators. Rather, the mention of ED is flanked by prostatic hypertrophy and hearing loss, which are not vascular disorders, and therefore would not cause a POSA to form a connection between ED and vasodilators.

119. Vice versa, the paragraph mentioning vasodilators does not mention ED. Rather, that paragraph (on page 18) states that the compounds of general formula I can be combined with several classes of drugs which “treat high blood

pressure or any cardiac disorders.” EX1004, 18. A POSA would not have understood Bolli to disclose PDE5 inhibitors from the separate, unrelated mentions of “vasodilators” in one part of Bolli and ED in a different part of Bolli.

120. Also, while Bolli teaches that the described compounds of formula I may be used to treat ED, it does not additionally teach the use of the described compounds *in combination with* drugs that also treat ED. For example, Bolli does not discuss drugs that were known to treat ED, such as PDE5 inhibitors, or prostaglandins, and certainly does not teach that the compounds of general formula I could be combined with such drugs. Thus, the mention of ED is completely removed from the mention of “vasodilators,” and a POSA would not have considered these two concepts together in the context of Bolli.

121. Dr. Shebuski is further mistaken that a POSA’s knowledge of sildenafil and tadalafil means a “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.” EX1013, ¶ 99. Rather, the omission of PDE5 inhibitors like sildenafil and tadalafil, especially in light of the disclosure of ED, would have led a POSA to understand that Bolli does *not* disclose PDE5 inhibitors.

C. The '847 Patent Claims Would Not Have Been Obvious Over Bolli in View of Keyser

122. I have also been asked to consider the '847 patent and the Bolli and Keyser references to determine whether the claims would have been obvious in light of Bolli and Keyser. Based on my review, it is my opinion that the claims of the '847 patent would not have been obvious in light of Bolli and Keyser.

123. Dr. Shebuski argues: “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.” EX1013, ¶ 181.

124. I disagree. Because Keyser teaches away from using a dual, nonselective ERA (like macitentan) in combination with a PDE5 inhibitor, and Bolli additionally provides no motivation to select macitentan or combine it with a PDE5 inhibitor, a POSA would not be motivated to combine macitentan with a PDE5 inhibitor based on Bolli and Keyser. Even assuming a POSA would have combined macitentan with a PDE5 inhibitor based on these references (which is not the case), a POSA would not have reasonably expected to successfully arrive at the '847 patent’s claimed combination of macitentan and a PDE5 inhibitor for the

use in treatment of diseases involving vasoconstriction. Additionally, the unexpected results reported in the '847 patent support the non-obviousness of the claims. For at least these reasons, it is my opinion that Bolli and Keyser do not render obvious any of the claims of the '847 patent.

1. Keyser Teaches Away From Using a Nonselective ET_A/ET_B Antagonist with a PDE5 Inhibitor

125. As discussed above, macitentan is a dual, or nonselective ERA.

¶¶ 58-65. Thus, turning to Keyser, which teaches combining *ET_A-selective* antagonists with PDE5 inhibitors, it is my opinion that these teachings would have led a POSA *away* from the '847 patent's claimed inventions comprising macitentan in combination with PDE5 inhibitors.

126. As I have summarized above, Keyser focuses on the combination of ET_A-selective antagonists with PDE5 inhibitors. ¶¶ 90-95. Keyser states that its “invention relates generally to combination therapies comprising an endothelin A receptor (ET_A) antagonist and a phosphodiesterase 5 (PDE5) inhibitor,” and describes various “embodiments” that all include a combination of an ET_A antagonist with a PDE5 inhibitor. EX1005, 2, 6-9. The examples of Keyser are also about the combination of an ET_A antagonist, sitaxsentan, with a PDE5 inhibitor, sildenafil. *Id.*, 28-31.

127. Keyser additionally provides strong physiological reasons to target the ET_A pathway using an ET_A-selective antagonist, while also using a PDE5 inhibitor.

¶¶ 92-94. Keyser outlines:

- “Within the cardiovascular system, the effects of ET-1 on vascular smooth muscle cells and cardiac myocytes are believed to be principally mediated through the ET_A.” EX1005, 16.
- “Use of a nonselective ET receptor interferes with multiple pathways whereas use of a specific ET_A antagonist will act in a complementary fashion for the multiple pathways (PDE and/or prostacyclin and/or ET_A) to provide superior efficacy and/or dosage regimes and/or reduction in side effects.” *Id.*, 20.
- “The mechanism by which ET_B causes vasodilatation is through stimulating the production of nitrous oxide and prostacylin. Nitrous [*sic*, nitric] oxide (NO) in turn activates the guanyl cyclase which increases the level of cGMP. The cGMP is responsible for relaxing the blood vessel PDE5 acts to break down cGMP, so a PDE5 inhibitor also raises the level of cGMP, causing vasodilatation. Thus, when used together, increasing cGMP through the ET_A receptor and preventing its breakdown leads to increased vasodilatation and better efficacy of both drugs.” *Id.*, 20-21.

- “Nonselective antagonists would not function as effectively because they block the ET_B stimulated cGMP production.” *Id.*, 21.

128. Simply put, Keyser teaches that use of a ET_A-selective antagonist in combination with a PDE5 inhibitor will act in a complementary fashion because (1) the ET_A-selective antagonist will reduce vasoconstriction by inhibiting ET-1’s binding to the ET_A receptor; (2) the ET_A-selective antagonist will not interfere with ET-1’s binding to the ET_B receptor on endothelial cells, and thereby will not interfere with the ET_B receptor’s stimulation of cGMP, a protein responsible for vasodilation; and (3) the PDE5 inhibitor will prevent the breakdown of cGMP caused by PDE5, leading to vasodilation.

129. By contrast, Keyser teaches that a nonselective antagonist would not be as effective because it would interfere with the ET_B receptor’s ability to stimulate cGMP production, thereby lessening its vasodilatory effects. In turn, this would impede or render useless the effects of the PDE5 inhibitor, which only works to prevent the breakdown of cGMP.

130. Thus, Keyser would discourage a POSA from using a nonselective, or dual, antagonist with a PDE5 inhibitor.

2. Macitentan Is a Nonselective ET_A/ET_B Antagonist

131. I disagree with Dr. Shebuski’s argument that macitentan is a “selective ET_A antagonist.” EX1013, ¶ 374. Dr. Shebuski focuses on Keyser’s

selectivity ratio for an ET_A-selective antagonist and argues that macitentan falls within Keyser's criteria for an ET_A-selective antagonist, or in the alternative, that a POSA would expect macitentan to fall within Keyser's criteria for an ET_A-selective antagonist based on Bolli's disclosure of a different compound, Example 104. EX1013, ¶¶ 358-374. For the reasons below, both arguments are incorrect. Based on Keyser's teachings, a POSA would come to the *opposite* conclusion, which is that Keyser would categorize macitentan as a nonselective antagonist.

132. Keyser sets forth a criteria for ET_A-selective antagonists:

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, 25000, etc., if they are going to act at only one of the receptor subtypes, e.g. ET_A.***

EX1005, 16 (emphasis added).

133. Keyser then contrasts a nonselective antagonist, bosentan, which has a selectivity ratio of 20, with sitaxsentan which has a selectivity ratio of 6500, stating that “for the purposes of this invention, bosentan or any other non-specific endothelin receptor antagonist would not represent an ET_A-specific antagonist.”

EX1005, 16-17.

134. Keyser provides examples of nonselective and ET_A-selective antagonists in Tables 2 and 3. Both tables lists various compounds that were in pre-clinical or clinical development as of 2000. EX1005, 17-18 (citing Luscher et

al., *Endothelin and Endothelin Receptor Antagonists: Therapeutic Considerations for a Novel Class of Cardiovascular Drugs*, CIRCULATION, 2000 Nov

7;102(19): 2434-40). Table 2 provides, for certain compounds, the ET_A and ET_B receptor binding values (reported as K_i values), as well as the selectivity ratio which is found by dividing the K_i value for ET_B by the K_i value for ET_A. *Id.*, 19. Table 3 then classifies certain compounds as either ET_A-selective or ET_A/ET_B-nonselective. *Id.*

135. There is significant overlap between the compounds that are listed in Table 2 and the compounds that are listed in Table 3, so it makes sense to assess the two tables together. Below, I have reproduced Table 2 on the left and Table 3 on the right. Highlighted in green below are the compounds that Keyser labels as ET_A-selective antagonists. All of these have a selectivity ratio of at least 1000.

Compound	ET _A	ET _B	Selectivity
ABT-627	0.034	63.3	1862
ABT-646	0.46	13,000	28,261
BMS-182874	48	>50,000	>1000
FR-139317	1.0	7300	7300
J-104132	0.034	0.1	2.9
LU-135252	1.4	184	130
PD-156707	0.17	139	818
Bosentan	6.5	343	53
Ro-61-1790	0.13	>130	1000
S-0139	1.0	1000	1000
SB-209670	0.20	18	90
SB-217242	1.1	111	101
T-0201	0.015	41	2700
TAK-044	1.3	590	454
TBC-11251	0.43	>4300	10,000
ZD-1611	1.3	>2000	1500

Compound	Selectivity
ABT-627	ET _A
BMS-182874	ET _A
BMS-193884	ET _A
FR-139317	ET _A
J-104132/1-753037	ET _A /ET _B
LU-135252	ET _A /ET _B
Bosentan	ET _A /ET _B
Ro-48-5695	ET _A
Ro-61-0612	ET _A
Ro-61-1790	ET _A
S-0139	ET _A
SB-209670	ET _A /ET _B
SB-217242	ET _A /ET _B
TAK-044	ET _A /ET _B
TBC-11251	ET _A
ZD-1611	ET _A

136. Highlighted in blue below are the compounds that Keyser labels as nonselective ET_A/ET_B antagonists. In contrast to the compounds shown above, these all have a selectivity ratio less than 1000.

Compound	ET _A	ET _B	Selectivity
ABT-627	0.034	63.9	1862
ABT-646	0.46	13,000	28,261
BMS-182874	48	>50,000	>1000
FR-139317	1.0	7300	7300
J-104132	0.034	0.1	2.9
LU-135252	1.4	184	130
PD-156707	0.17	139	818
Bosentan	6.5	343	53
Ro-61-1790	0.13	>130	1000
S-0139	1.0	1000	1000
SB-209670	0.20	18	90
SB-217242	1.1	111	101
T-0201	0.016	41	2700
TAK-044	1.3	690	454
TBC-11251	0.43	>4300	10,000
ZD-1611	1.3	>2000	1500

Compound	Selectivity
ABT-627	ET _A
BMS-182874	ET _A
BMS-183884	ET _A
FR-139317	ET _A
J-104132/L-753037	ET _A /ET _B
LU-135252	ET _A /ET _B
Bosentan	ET _A /ET _B
Ro-48-5685	ET _A
Ro-61-0612	ET _A
Ro-61-1790	ET _A
S-0139	ET _A
SB-209670	ET _A /ET _B
SB-217242	ET _A /ET _B
TAK-044	ET _A /ET _B
TBC-11251	ET _A
ZD-1611	ET _A

137. Based on these teachings, a POSA would understand Keyser to be providing a criteria for selectivity in which ET_A-selective antagonists have a selectivity ratio of over 1000 and nonselective ET_A/ET_B antagonists have a selectivity ratio of less than 1000.

138. I thus disagree with Dr. Shebuski's opinion that a "POSA would have understood . . . 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)."

EX1013, ¶ 363. Keyser does not merely state a "preference" for ET_A-selective antagonists, and certainly does not teach that the ERA has to only be more selective for ET_A than bosentan. Keyser's own tables label multiple compounds as ET_A/ET_B dual antagonists that are more selective for ET_A than bosentan. Keyser states LU-135252 has a selectivity of 130, SB-209670 has a selectivity of 90, SB-217242 has a selectivity of 101, and TAK-044 has a selectivity of 454. All of these are labeled as dual ET_A/ET_B antagonists and have selectivity ratios greater

than bosentan, which has a selectivity of 53 (according to table 2) or 20 (according to other sections of Keyser). EX1005, 16-19. Keyser does not provide any example of an ET_A-selective antagonist with a ratio less than 1000. Also, as explained above, Keyser indicates that all nonselective ET_A/ET_B antagonists are unfavored, not just those that are at or below bosentan's selectivity for ET_A.

139. Bolli does not provide the selectivity ratio of macitentan, but it was reported elsewhere (in Iglarz and Bolli 2012) that macitentan has a selectivity ratio of 782. EX1011, 6; EX1024, 6-7. Thus, under Keyser's criteria, macitentan would be considered a nonselective ET_A/ET_B antagonist. Based on Keyser's teachings, a POSA would not expect a combination of such a nonselective ET_A/ET_B antagonist with a PDE5 inhibitor to exhibit the same efficacy as a combination of an ET_A-selective antagonist with a PDE5 inhibitor, given that blocking ET_A and ET_B together would decrease ET_B-stimulated cGMP production and would impede the effects of PDE5, as Keyser cautions.

140. Dr. Shebuski also argues that a POSA would expect macitentan to fall within Keyser's criteria for an ET_A-selective antagonist based on Bolli's disclosure of a different compound, Example 104. EX1013, ¶¶ 365-367. Bolli reports that Example 104 has an IC₅₀ value for ET_A of 0.88 and an IC₅₀ value for ET_B of 601, meaning that the selectivity ratio would be 683. EX1004, 7. Under Dr. Shebuski's argument, even if Example 104 could be compared to macitentan (and I do not

agree that it is comparable), Example 104 would still be classified by Keyser as a nonselective ET_A/ET_B antagonist, based on the criteria discussed above.

141. However, Dr. Shebuski has not provided any reason why a POSA would even look to Example 104, which is not macitentan, as an indicator of macitentan's properties. As I previously explained, a POSA would not look to Example 104 as providing any relevant information about macitentan. ¶ 86.

3. A POSA Would Not Have Been Motivated to Combine Macitentan With A PDE5 Inhibitor Based on Bolli and Keyser

142. For at least the reasons above, a POSA would not have considered macitentan to be an ET_A-selective antagonist, and thus would not have been motivated to combine macitentan with PDE5 inhibitors based on Keyser.

143. Additionally, a POSA viewing Keyser as a starting point would not have chosen macitentan from Bolli. Bolli does not disclose or teach a preference for macitentan over any of the other compounds of general formula I. As I discussed above, macitentan is merely one of nearly 250 exemplary compounds that are disclosed by Bolli. ¶¶ 82-83. Bolli also provides no preclinical or clinical data regarding macitentan. For at least these reasons, I find Dr. Shebuski's statement that "Bolli teaches macitentan as one of its preferred endothelin receptor antagonist compounds" to be inaccurate. EX1013, ¶ 178.

144. A POSA starting from Bolli would not think to combine macitentan with a PDE5 inhibitor, because Bolli does not disclose combining any of its compounds (including macitentan) with PDE5 inhibitors. Bolli only includes *one sentence* about possibly combining compounds of general formula I with other drugs. EX1004, 18. As explained above in § VI.B, in this sentence, Bolli lists eight possible classes of drugs that may be combined with compounds of general formula I, and none of these eight classes of drugs is a PDE5 inhibitor. Dr. Shebuski focuses on Bolli's use of the word "vasodilators;" however, for the reasons discussed in the previous section, a POSA would not read "vasodilators" to include PDE5 inhibitors. ¶¶ 104-115. For at least these reasons, Bolli provides no motivation to combine macitentan with a PDE5 inhibitor.

145. A POSA starting with Keyser would have been taught the criteria for ET_A-selective antagonists that is summarized above. In particular, Keyser taught that ET_A-selective antagonists have a selectivity ratio of at least 1000.

146. Looking at the selectivity data provided in Bolli for Examples 1-214, there are only three compounds that fit Keyser's criteria for being an ET_A-selective antagonist, meaning they all have selectivity ratios of 1000 or greater. EX1004, 5-9. These are summarized in the table below.

Compound of Example	IC50 [nM]		Selectivity Ratio (ET _B / ET _A)
	ET _A	ET _B	
Example 24	2.2	2496	1135
Example 117	0.45	518	1151
Example 118	0.34	611	1797

147. In view of Keyser's teachings, a POSA would have chosen one of Example 24, Example 117, or Example 118. Bolli does not provide any motivation to use macitentan instead of any these compounds.

148. Given the clear instruction in Keyser that ET_A-selective antagonists should have a selectivity ratio of 1000 or greater, a POSA would not look to compounds with a lower selectivity ratio. However, to the extent Dr. Shebuski argues that an ERA only need to have a selectivity ratio of 100, *see, e.g.*, EX1013, ¶¶ 362-364, Bolli discloses more than 50 compounds that meet a selectivity ratio of at least 100. EX1004, 5-9. These are summarized in the table below.

Compound of Example	IC50 [nM]		Selectivity Ratio (ET _B / ET _A)
	ET _A	ET _B	
Example 12	59	>10000	>169
Example 14	5.6	1033	184
Example 15	18.5	2161	117
Example 16	45	8452	188
Example 18	8.5	3333	392
Example 19	25	3414	137
Example 20	4.9	1723	352
Example 21	7	1001	143
Example 23	3.6	1585	440
Example 24	2.2	2496	1135
Example 26	54	>10000	>185
Example 29	13.5	4230	313
Example 32	3.5	864	247

Compound of Example	IC50 [nM]		Selectivity Ratio (ET _B / ET _A)
	ET _A	ET _B	
Example 33	3.7	609	165
Example 34	23	3267	142
Example 61	1.6	200	125
Example 73	1.9	567	298
Example 80	10	>1000	>100
Example 100	0.76	283	372
Example 101	1.24	335	270
Example 102	0.46	65	141
Example 104	0.88	601	683
Example 105	0.69	203	294
Example 107	0.25	96	384
Example 108	0.28	56	200
Example 109	1.94	>1000	>515
Example 110	2.3	>1000	>435
Example 111	12.3	3750	305
Example 112	0.52	257	494
Example 113	4.26	581	136
Example 114	8.3	>1000	>120
Example 115	2.2	>1000	>455
Example 116	1.3	567	436
Example 117	0.45	518	1151
Example 118	0.34	611	1797
Example 119	4.2	>1000	238
Example 133	1.7	212	125
Example 145	1.64	>1000	610
Example 146	5	514	103
Example 147	1.2	408	340
Example 160	11	3221	293
Example 161	6.2	>1000	161
Example 163	0.44	80	182
Example 184	29.5	3777	128
Example 193	3.6	>1000	278
Example 194	9.5	>1000	105
Example 196	4.4	>1000	227
Example 197	1.16	418	360
Example 212	3.1	>1000	323
Example 213	1.32	347	263

Compound of Example	IC50 [nM]		Selectivity Ratio (ET _B / ET _A)
	ET _A	ET _B	
Example 214	0.76	241	317

149. Notably, none of the compounds listed above is macitentan. Among the examples listed above, Bolli also offers no guidance as to which of the compounds to pick, at least because Bolli does not describe use of any compounds in combination with PDE5 inhibitors. Importantly, Bolli provides no motivation to choose macitentan instead of one of these exemplary compounds. Therefore, for at least these reasons, it is my opinion that a POSA starting from Keyser and looking to Bolli would not have been motivated to select macitentan, and certainly would not have been motivated to combine macitentan with a PDE5 inhibitor.

4. A POSA Would Not Have Combined Bolli and Keyser's Teachings With A Reasonable Expectation of Success

150. Even if a POSA were to combine the teachings of Keyser and Bolli, they still would not have a reasonable expectation of success of achieving the claimed inventions, which involve the use of macitentan in combination with a PDE5 inhibitor to treat diseases involving vasoconstriction.

151. Keyser offers no examples of the combination of nonselective, or dual, antagonists with PDE5 inhibitors. In fact, the only mention of a dual antagonist with a PDE5 inhibitor was "a recent study" in which "Bosentan, a non-selective antagonist was tested with sildenafil." EX1005, 21. However, Keyser

states this study “was terminated due to pharmacokinetic drug interaction problems.” That is consistent with the understanding of a POSA at the time, as bosentan was known to have poor pharmacokinetic drug-drug interactions with other therapies, including sildenafil. *See, e.g.*, EX2032, 112 (“[B]osentan significantly decreases the plasma concentration of sildenafil when coprescribed to patients with pulmonary hypertension. This interaction would be expected to undermine the potential benefits of combining the two drugs”).

152. The examples in Keyser also offer no reasonable expectation of success. Example 1 of Keyser discusses a pharmacokinetic drug interaction study in which 12 healthy individuals received 100 mg of sitaxsentan for seven days and 100 mg of sildenafil on the last day. EX1005, 28. Another 12 healthy individuals received a placebo for seven days and 100 mg sildenafil on the last day. *Id.* The subjects’ blood was drawn in order to determine blood plasma levels of sitaxsentan and sildenafil. *Id.* The results of the experiment showed that “sildenafil administration did not alter sitaxsentan levels” and that sildenafil did not affect the pharmacokinetics of sitaxsentan. *Id.*, 28-29.

153. Dr. Shebuski relies on Example 1 to show that a “POSA would [] have reasonably expected that macitentan and a PDE5 inhibitor to be a safe drug combination which is capable of lowering blood pressure.” EX1013, ¶ 189. However, Example 1 only showed that sitaxsentan and sildenafil demonstrated no

negative pharmacokinetic drug interactions. Example 1 did not teach that the combination lowered blood pressure. Keyser did not test the combination in patients with increased blood pressure, or otherwise report any data demonstrating the effects of sitaxsentan and sildenafil on lowering blood pressure. Thus, Example 1 provides no reasonable expectation about the efficacy of the tested combination to treat diseases involving vasoconstriction.

154. Moreover, Dr. Shebuski's argument relies on an incorrect premise that macitentan is an ET_A-selective antagonist. As explained above, macitentan is a dual antagonist. ¶¶ 58-66, 131-141. On the other hand, sitaxsentan is a highly selective ET_A antagonist, with a selectivity ratio of 6,500. EX1005, 16. A POSA would not expect that replacing sitaxsentan with macitentan in the combinations of Keyser would have similar results, at least in light of Keyser's teachings that nonselective antagonists do not work as effectively as ET_A-selective antagonists.

155. Example 2 of Keyser purports to present an "Efficacy Study," but it is only a plan for a study, without any data. EX1005, 30-31. Keyser states that a "randomized, double-blind, placebo-controlled study is performed comprising 60 subjects who have moderate to severe pulmonary arterial hypertension." *Id.*, 30. The patients will be given sitaxsentan in combination with sildenafil, or placebo, and "6 minute walking distance tests are conducted to evaluate the change in the subjects' exercise capacity," while "symptoms of PAH are evaluated." *Id.* Keyser

hypothesizes that “[m]inimal drug interaction and side effects with treatment *will occur* in the combination . . . groups . . . while maintaining successful therapeutic effect.” *Id.* 31 (emphasis added). However, Keyser does not provide any results actually demonstrating successful therapeutic effect.

156. Thus, the examples in Keyser, even in view of Bolli’s disclosure, would not convey to a POSA a reasonable expectation of success for a combination of macitentan and a PDE5 inhibitor.

157. For at least the reasons discussed above, the claims of the ’847 patent would not have been obvious from Bolli in combination with Keyser.

5. Unexpected Results Support The Non-Obviousness of the ’847 Patent Claims

158. As detailed above, the Examples in the ’847 patent each describe a combination of macitentan and a PDE5 inhibitor (either sildenafil or tadalafil) and demonstrate that the combination resulted in a synergistic therapeutic effect in the reduction of blood pressure. ¶¶ 72-74. These unexpected results reported in the ’847 patent support the non-obviousness of the claims.

159. These results would have been unexpected and surprising, at the time of the ’847 invention, at least because of the prior art’s, specifically Keyser’s, teachings that nonselective ET_A/ET_B antagonists (like macitentan) do not work effectively with PDE5 inhibitors.

160. I therefore disagree with Dr. Shebuski and UT that a POSA would have expected synergy between macitentan and a PDE5 inhibitor. Dr. Shebuski argues that 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.” EX1013, ¶ 394. There are multiple issues with this argument.

161. First, a POSA would not necessarily expect that a combination of drugs targeting multiple pathways to exhibit synergistic therapeutic effect. Synergistic therapeutic effect is defined as an effect of two therapies in combination being greater than the sum of their individual therapeutic effects. This is often discussed in comparison to additive effect, which is when the combined outcome of the therapies equals the sum of the individual effects.

162. Using a combination therapy that targets multiple different pathways may be a strategy to increase the probability of a response in a particular individual. A range of outcomes may occur, from simple additive effect to a personalized response based on a patient’s specific biology or genetics. Synergy may also occur in some individuals who are sensitive to both pathways, but it would not be expected. On the other hand, a patient may not respond at all to combination therapy, or there may be adverse effects.

163. Second, a POSA would not expect synergistic effect in targeting multiple pathways within the vascular system. In particular, because the ET_B receptor has both vasoconstrictive and vasodilatory effects, and also plays a role in ET-1 clearance, there may be negative aspects to ET_B blockade, such as through a dual ERA. It is unclear whether adding a PDE5 inhibitor would effectively and reliably overcome those negative aspects of ET_B receptor blockade.

164. Indeed, it was known that targeting multiple pathways or using drugs with different mechanisms of actions could result in negative drug interactions, like bosentan and sildenafil, *see, e.g.*, EX2032, 112, or result in weakening or hindering the efficacy of one or both of the agents, as explained in Keyser. EX1005, 20-21; *see also* EX2026, 405. Because of the potential issues caused by targeting multiple pathways, particularly within the vascular system, a POSA certainly would not expect synergistic therapeutic effect.

165. Third, an expectation that a drug combination is “complementary” does not equate to an expectation that the combination will have “synergy.” Complementary is not a formal classification of a drug interaction. If two drugs are said to be “complementary,” that would just mean that the two drugs may complement each other in some way, or they may work well together. It does not convey any degree of therapeutic effect. While two treatments may be

complementary, there is no expectation that the therapies would demonstrate any synergistic therapeutic effect.

166. Thus, Keyser's teaching that "use of a specific ET_A antagonist will act in a complementary fashion for the multiple pathways (PDE and/or prostacyclin and/or ET_A) to provide superior efficacy and/or dosage regimes and/or reduction in side effects teachings" does not convey any expectation of synergy. EX1005, 20.

167. Finally, even if two therapies were thought to be complementary, or had the potential for complementary action, that would at most signal to a POSA that the combination *might* be worth trying, but it would not convey any reasonable expectation of success that the combination would have any therapeutic effect, let alone a synergistic therapeutic effect.

168. A POSA would only gain a reasonable expectation of synergy through actual data which demonstrates such synergy, such as the data reported in the examples in the '847 patent. At least before the '847 patent, which was the first disclosure of macitentan in combination with a PDE5 inhibitor, there were no such data demonstrating synergy between macitentan and a PDE5 inhibitor, and the prior art at the time did not suggest synergy.

D. The '847 Patent Claims Would Not Have Been Obvious Over Bolli, Hoeper, and Morice

169. I have been asked to consider the '847 patent and the Bolli, Hoeper, and Morice references to determine whether the claims would have been obvious

in light of them. Based on my review of Hoeper and Morice, these references appear to be duplicative of the teachings of Keyser. Thus, for at least similar reasons discussed above with respect to the Bolli and Keyser combination, and for the additional reason that neither Hoeper nor Morice offers any motivation to use macitentan in combination with a PDE5 inhibitor, it is my opinion that the combination of Hoeper, Morice, and Bolli would not render obvious the claims of the '847 patent.

170. As I summarized above, Hoeper presents preliminary data from nine patients with severe IPAH who took bosentan and sildenafil. EX1009, 1; ¶¶ 97-100. Morice only adds the experience of one patient with IPAH who first took bosentan and sildenafil, and then later took bosentan and tadalafil. EX1010, 1; ¶ 101-102. Keyser also discloses that bosentan was tested in combination with sildenafil. EX1005, 21. Therefore, Hoeper and Morice do not add anything new to what Keyser discloses.

171. A POSA would not be motivated to combine Bolli, Hoeper, and Morice, and the combination of these references would not lead a POSA to the claimed invention. As I have previously discussed, Bolli discloses compounds of general formula I which includes macitentan, but does not teach or even suggest that any compounds in this class (including macitentan) should be combined with a PDE5 inhibitor. ¶ 144. Bolli also does not encourage the use of macitentan over

any of the other compounds of formula I that are described therein. Hoeper and Morice only discuss a combination of bosentan with either sildenafil or tadalafil, and do not teach anything about macitentan or suggest the use of other ERAs in combination with sildenafil or tadalafil. Therefore, contrary to Dr. Shebuski's opinion, a POSA would **not** have considered the teachings of Hoeper and Morice together with the teachings of Bolli. EX1013, ¶ 273.

172. Even assuming a POSA combined the teachings of Bolli, Hoeper, and Morice, a POSA would not have been motivated to swap bosentan with macitentan, and certainly would not do so in combination with a PDE5 inhibitor. Dr. Shebuski argues that a "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 know bosentan to have only minimal selectivity for ET_A over ET_B. . . . Macitentan, on the other hand, was understood by the POSA to be highly selective for ET_A over ET_B. . . ." EX1013, ¶ 285.

173. Dr. Shebuski's explanation as to *why* a POSA would want to substitute bosentan with an ET_A-selective antagonist is unsubstantiated. EX1013, ¶ 284. As I explained above, Bolli does not teach that macitentan is more selective for ET_A over ET_B. ¶¶ 85-86, 139-140. Additionally, neither Bolli nor Hoeper/Morice teach that ET_A-selective antagonists should be used instead of dual

or nonselective antagonists. The only asserted reference that teaches about the benefits of ET_A-selective antagonists over nonselective antagonists is Keyser. *See* EX1005, 20-21. The suggested rationale for substituting bosentan with macitentan is the same as what Keyser teaches: it is beneficial to use an ERA that is selective for ET_A (with a selectivity ratio of 1000:1), rather than a nonselective ERA. These arguments would then fail for the same or similar reasons I have discussed above with respect to the combination of Bolli and Keyser. *See* § VI.C. Macitentan is a dual antagonist, and Keyser teaches away from using dual antagonists in combination with PDE5 inhibitors. *Id.*

174. Even if a POSA would have combined the teachings of these references, a POSA would not have done so with a reasonable expectation of success. Hoeper provides an “observational report” showing the effects of the combination of bosentan and sildenafil on nine patients. EX1009, 3. There are two types of observations that are reported: 6-minute walk distance and CPET (cardiopulmonary exercise training) data. EX1009, 2-3. The authors observed that in patients who took bosentan with sildenafil, 6-minute walk distance was slightly higher than baseline and oxygen uptake was increased. *Id.* This does not suggest a degree of therapeutic efficacy of the combination therapy, only that sildenafil *may* rescue a failing patient on bosentan. In addition, this observational study was conducted in an open-label or unblinded fashion, which is open to major biases by

the patient and the investigator (such as subjective assessments or observations about efficacy). Indeed, Hoeper reports no data regarding the reduction of pulmonary blood pressure in these patients.

175. Based on these observations, Hoeper hypothesizes that “combining bosentan and sildenafil *might* be feasible in patients with IPAH,” but notes that the study has “several inherent limitations,” including lack of control group, small patient population, and limited observation period. *Id.*, 3.

176. Morice only adds the experience of *one* patient who took bosentan and tadalafil, and experienced a decrease in pulmonary blood pressure, at least compared to bosentan alone. EX1010, 1.

177. The case studies in Hoeper and Morice therefore do not provide sufficient evidence to conclude that the combination of bosentan and sildenafil or bosentan and tadalafil would be successful to treat patients with PAH. More fundamentally, these studies provide no insight into whether other ERAs could similarly be combined with sildenafil or tadalafil to treat PAH. For example, Hoeper concludes: “it is unknown whether combination treatment is truly more efficient than single treatment (although theoretical reasoning clearly favours combination treatment, switching to sildenafil may have been equally effective as combining bosentan and sildenafil).” EX1009, 4. Such uncertainty would not convey a reasonable expectation of success to a POSA.

VII. Conclusion

178. For the reasons above, it is my opinion that the '847 patent claims would not have been anticipated by Bolli, would not have been obvious over Bolli in view of Keyser, and would not have been obvious over Bolli, Hoeper, and Morice.

179. This declaration is based on information currently available to me. I have also been informed that this declaration is being submitted solely in conjunction with Actelion's Preliminary Response to UT's Petition. As such, my declaration should not be construed as a full and complete response to UT's Petition or the declaration submitted by Dr. Shebuski. If UT's Petition for *inter partes* review is granted, I reserve the right to supplement this declaration or submit a new declaration in order to include or respond to additional arguments made by UT or Dr. Shebuski.

I, Dr. Luke Howard, DPhil MB BChir FRCP, do hereby declare and state, 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, under Section 1001 of Title 18 of the United States Code.



Dr. Luke Howard, DPhil MB BChir FRCP

October 1, 2025
Date

APPENDIX A

Professor Luke Howard MA DPhil MB BChir FRCP

Consultant Pulmonologist

Professor of Practice (Cardiopulmonary Medicine)

Curriculum vitae

Full name: Luke Sebastian Geoffrey Eliot Howard

Nationality: British

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GMC Number: 4370576

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Private PA : Mrs Lucia Heath

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Medico-legal PA : Mrs Elizabeth Howard

e-mail : omfxbh@gmail.com

Web sites:

<http://www1.imperial.ac.uk/medicine/people/l.howard/>

YouTube Channel:

<http://tinyurl.com/Dr-Luke-Howard>

On-line Prezi repository:

<http://tinyurl.com/LukeHoward-Prezi>

Twitter: @HelpMyBreathing

Employment

Current

9/21–	Professor of Practice (Cardiopulmonary Medicine), National Heart & Lung Institute, Imperial College London
9/17–	Director – National Pulmonary Hypertension Service, Hammersmith Hospital, Imperial College Healthcare NHS Trust
9/08–	Lead Clinician – Exercise Physiology Service, Hammersmith Hospital, Imperial College Healthcare NHS Trust
5/06–	Consultant Pulmonologist with an interest in Pulmonary Hypertension, Hammersmith Hospital, Imperial College Healthcare NHS Trust (Director of Service since 9/17)
8/17–	Honorary Consultant Physician, Barts Health NHS Trust, London
11/10–	Honorary Consultant Physician, Bristol Royal Infirmary

Previous

5/06–9/21	Honorary Clinical Senior Lecturer, National Heart & Lung Institute, Imperial College London
2/06–5/06	SpR, Respiratory/GIM, QE2 Hospital, Welwyn Garden City
12/04–2/06	British Heart Foundation Junior Research Fellow, Department of Medicine, University of Cambridge
9/04–12/04	SpR, Respiratory/GIM, Norfolk & Norwich University Hospital
9/03–9/04	SpR, Respiratory/GIM, Addenbrooke's Hospital, Cambridge
3/03–9/03	SpR, Transplant Medicine, Papworth Hospital, Cambridge
9/02–3/03	SpR, Pulmonary Vascular Diseases, Papworth Hospital, Cambridge
6/01–9/02	SpR, Respiratory/GIM, Norfolk & Norwich University Hospital
2/01–6/01	SpR (LAT), Medical Admissions Unit, Addenbrooke's Hospital, Cambridge
8/00–2/01	SHO Anaesthetics, Norfolk & Norwich University Hospital
2/00–8/00	SHO General/Metabolic Medicine, Addenbrooke's Hospital, Cambridge
8/99–2/00	SHO Intensive Care Medicine, Guy's and St Thomas's Hospital, London
2/99–8/99	SHO Renal Medicine, Guy's Hospital, London
8/99–2/99	SHO Cardiology, St Thomas's Hospital, London
2/98–8/98	SHO Respiratory Medicine, Royal Brompton Hospital, London
8/97–2/98	HO General Surgery, Bedford Hospital
2/97–8/97	HO General/Metabolic/Elderly Medicine, Addenbrooke's Hospital, Cambridge
9/87–7/88	Research Officer at Histochemistry Dept (Professor Julia Polak), Royal Postgraduate Medical School, London

Private Admitting/Practicing Rights

Sainsbury Wing, Hammersmith Hospital, Imperial College Healthcare NHS Trust

The Physicians' Clinic (Harley Street Clinic (HCA Healthcare)), 13-14 Devonshire Street,
London W1G 7AE

OneWelbeck Lung Health, 1 Welbeck St, London, W1G 0AR

Education

1994–96	JESUS COLLEGE, UNIVERSITY OF CAMBRIDGE MB BChir
1988–94	CHRIST CHURCH, UNIVERSITY OF OXFORD DPhil Physiological Sciences BA (Hons) Physiological Sciences: 2.1
1983–87	ST PAUL'S SCHOOL Senior Scholar

Selected Prizes and Awards

2021	National Clinical Excellence Award (Gold)
2017	National Clinical Excellence Award (Silver)
2015	American Thoracic Society Travel Scholarship awarded for research
2013	National Clinical Excellence Award (Bronze)
1994–96	William Harvey Scholarship, University of Cambridge

Other Qualifications

May 2010	Fellowship of Royal College of Physicians
Oct 1999	Membership of Royal College of Physicians

Teaching Responsibilities

2008–12	Lecturer for Imperial College MRes course
2006–	Lecturer for Imperial College School of Medicine
2006–10	Lecturer for Diploma in Cardiology, Imperial College

2003–6	Clinical Supervisor, Jesus College Cambridge.
2000	Clinical Supervisor, Jesus College Cambridge. Awarded ‘Supervisor of the year’ (7 distinctions and Medical Prize and Surgical Prize gained in Final MB).
1992–1994	Tutor in Physiological Sciences and Human Sciences (Preliminary examinations) for eight colleges, University of Oxford Tutor for Final Honours School in Respiratory Physiology, University of Oxford

Current / Recent Research Grants

Apr 24	Determine the role of HIF2 α signalling in the systemic metabolic phenotype associated with the development of pulmonary hypertension. (Co-investigator; Chief Investigator for clinical sub-study). British Heart Foundation. PG/23/11488.
Feb 20 -	Positioning Imatinib for Pulmonary Arterial Hypertension (Co-investigator; CI Prof Martin Wilkins). NIHR EME Precision Medicine Award NIHR128465. £1,232,879.27.
Jan 19 -	National cohort study of idiopathic and heritable pulmonary arterial hypertension. (Co-investigator; PI Prof Nicholas Morrell). British Heart Foundation Programme Grant. £1,826,905. SP/18/10/33975.
Apr 18 -	Oxygen-enhanced MRI of the lungs for the evaluation of pulmonary hypertension (Co-investigator). NIHR Imperial Biomedical Research Centre. P74324 / PSF168 £57,000.

Prior Research Grants

2010 - 17	Iron homeostasis in pulmonary arterial hypertension. British Heart Foundation Programme grant (Co-investigator; PI Prof Martin Wilkins). Chief Investigator for Multicentre Clinical Study. RG/10/16/28575 £1,038,294.
2010 – 15	Physiological and haematological characteristics of unresolved pulmonary embolism – registry outcomes of a 5-year multidisciplinary follow-up approach. (Principal Investigator, co-investigator Dr Nina Salooja). Bayer. £240k
2013 – 15	Does exercise-MRI predict response to therapy in pulmonary hypertension? (Co-investigator; PI Dr D O'Regan). British Heart Foundation. PG/13/44/30321 £232,551.
2012–13	Acute pulmonary haemodynamic effects of apelin in pulmonary hypertension. (Co-investigator; PI Prof AJ Peacock). British Heart Foundation. PG/11/113/29280 £201,508

- 2011-13 Improving the ability of the cardiopulmonary exercise test to distinguish between cardiovascular and respiratory components of functional limitation. (Co-investigator; PI Dr Roland Wensel). British Heart Foundation. PG/11/36/28883 £178,348
- 2010-12 Role of endothelium in pathogenesis of chronic thromboembolic pulmonary hypertension. (Co-investigator; PI Dr Sarah Mangles). Baxter / Royal College of Pathologists Fellowship. £140k.
- 2010-12 Novel exercise end-points in pulmonary hypertension. (Principal Investigator). Pfizer. £171k
- 2009-11 Inflammatory pathways in the pathogenesis of pulmonary vascular remodelling in PAH: The role of glucocorticoids and NF-kB signaling. (Co-investigator; PI Dr Stephen J Wort, co-investigator Prof Ian Adcock). British Heart Foundation FS/09/043/28040. £140,483.
- 2009-11 A randomised controlled trial of Dichloroacetate in Pulmonary Arterial Hypertension. (Co-investigator; PI Prof Martin Wilkins, co-investigator Dr JSR Gibbs). Medical Research Council £333k
- 2008 Development of protocol for pulmonary hypertension echocardiography. (Principal Investigator) Actelion Pharmaceuticals. £27k
- 2008 The role of steroid resistance in vascular remodelling in pulmonary arterial hypertension in humans and animal models, European Respiratory Society Long-Term Research Fellowship for Dr Laura Price. €28k
- 2008 Physiological characterisation of dysfunctional breathing disorder using cardiopulmonary exercise testing, real-time plethysmography and physiotherapeutic assessment. Hammersmith Hospital Trust Research Committee. (Supervisor). £4k
- 2006 Endothelial progenitor cell expression of BMP Type 1 and 2 receptors and synthesis of endothelin-1 in patients with pulmonary arterial hypertension. (Principal Investigator). Hammersmith Hospital Trust Research Committee. £10k

Single / Multicentre Studies / Trials – Steering Committee Member / Chief Investigator

- 2024- ViTAL-PH study. A Phase 2, Multicentre, Open-Label Trial to Evaluate APL-9796 in Adult Participants with Pulmonary Hypertension. Steering Committee member.
- 2023- PROSERA study. Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Clinical Study to Evaluate the Efficacy of Oral Inhalation of GB002 for the Treatment of WHO Group 1 Pulmonary Arterial Hypertension (PAH). Steering Committee member.

- 2021- TORREY study. Phase 2, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Clinical Study to Evaluate the Efficacy and Safety of Oral Inhalation of GB002 for the Treatment of WHO Group 1 Pulmonary Arterial Hypertension (PAH). Steering Committee member.
- 2019-20 Phase 1B, randomized, blinded, placebo-controlled, multi-center clinical trial to evaluate the safety, pharmacokinetics (PK), pharmacodynamics (PD), and biomarkers of inhaled GB002 in adults with WHO Group 1 Pulmonary Arterial Hypertension (PAH). Gossamer Bio. Steering Committee member.
- 2017-19 Multicentre Retrospective Study of Hospital Length of Stay in Patients with Acute Pulmonary Embolism treated with Apixaban compared with Vitamin K Antagonists in the United Kingdom. Bristol-Myers Squibb. Steering Committee member.
- 2016-19 TRACE study. A multi-center, double-blind, placebo-controlled Phase 4 study in patients with pulmonary arterial hypertension to assess the effect of selexipag on daily life physical activity and patient's self-reported symptoms and their impacts. Actelion Pharmaceuticals. Steering Committee member. UK Chief Investigator.
- 2015-18 Clinical evaluation of the Therapeutic Intra-Vascular Ultrasound (TIVUS™) System for pulmonary artery denervation in patients with pulmonary hypertension. SoniVie. Steering Committee member. Chief Investigator (UK).
- 2014-17 MERIT-1/2 study. Prospective, randomized, placebo-controlled, double-blind, multicenter, parallel-group, 24-week study to assess the efficacy, safety and tolerability of macitentan in subjects with inoperable chronic thromboembolic pulmonary hypertension. Actelion Pharmaceuticals. Chief Investigator for UK. Steering committee member.
- 2011–2019 Multicentred, double-blinded, randomized, placebo-controlled trial of intravenous Ferric Carboxymaltose in idiopathic pulmonary arterial hypertension. British Heart Foundation. Chief Investigator. Steering Committee member.
- 2008–11 Multicentred, double-blinded, randomised, placebo-controlled trial of Bosentan in patients with pulmonary hypertension associated with idiopathic pulmonary fibrosis. Actelion Pharmaceuticals. Steering Committee member.

Research Supervision

- 2025- PhD co-supervisor (Dr Andrea Baccelli). Deep-phenotyping the response to drug treatment in PAH: the route to personalised medicine

2012-16	MD supervisor (Dr Geoff Watson). Multicentred, double-blinded, randomized, placebo-controlled trial of intravenous Ferric Carboxymaltose in idiopathic pulmonary arterial hypertension.
2010-12	Post-doctoral supervisor for Dr Bhashkar Mukherjee. Novel exercise end-points in pulmonary hypertension.
2008-11	PhD co-supervisor for Ka Hou Lao – Imperial College London (Division of Investigative Science). Endothelial Colony-Forming Cells in Patients with Idiopathic Pulmonary Arterial Hypertension.
2010-12	PhD co-supervisor for Dr Laura Price – Imperial College London (National Heart & Lung Institute). Inflammatory pathways in the pathogenesis of pulmonary vascular remodelling in PAH: The role of glucocorticoids and NF-κB signaling.
2012-13	MRes supervisor for Dr Svyatoslav Kechyn – Imperial College London. Effects of Apelin on kinetics of exercise in healthy man.
2011-13	MRes supervisor for Ms Susanne Fagerbrink – Imperial College London. The impact of non-resolved clot on quality of life post pulmonary embolism.
2011-12	MRes supervisor for Dr Akaphot Thongmee – Imperial College London. Effects of Apelin on exercise duration and peak performance in healthy man.
2008-9	MRes supervisor for Dr Zhenguo Zhai – Imperial College London. Physiological differences between pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension.
2009	BSc project supervisor for Alexandra Perkins – Imperial College School of Medicine. In-depth physiological characterization of patients with dysfunctional breathing. (awarded merit).
1993	BA project supervisor for Final Honours School dissertation student, University of Oxford. Hormonal response to 8 hours isocapnic and poikilocapnic hypoxia in man.

Committees

Selected Present Committees

2024-	Imperial College Representative to European Reference Network for rare respiratory diseases
2024-	Co-lead for Innovative Drug Development Initiative Pulmonary Vascular Research Institute

- 2017- Imperial College Healthcare NHS Trust Thrombosis Committee
- 2006- Member of National Pulmonary Hypertension Service Physicians Committee

Selected Past Committees

- 2019-23 Secretary, Pulmonary Hypertension Group (13.01), European Respiratory Society
- 2019-23 Member of Specialist Respiratory Clinical Reference Group, NHS England
- 2017-20 Chair, British Thoracic Society Standards of Care Committee
- 2017-20 Member, British Thoracic Society Board
- 2017-20 Trustee, British Thoracic Society
- 2012-17 Governor, Anscombe Bioethics Centre
- 2014-17 Member of End of Life Clinical Leadership Group for London. Chair for “Good Death” workstream
- 2013-5 Member of Specialist Advisory Group for Physiology to British Thoracic Society
- 2012-6 Pulmonary Hypertension Clinical Reference Group for NHS England
- 2011-14 European Society of Cardiology Working Group on Pulmonary Hypertension
- 2009-11 Member of Specialist Advisory Group for Pulmonary Circulation to British Thoracic Society
- 2009 NICE scoping committee for Apixaban in VTE prophylaxis in patients undergoing hip/knee replacement and in medical inpatients.
- 2003-6 Member of British Thoracic Society Standards of Care Committee
- 2003-6 Member of British Thoracic Society Council

Guideline Development

European Respiratory Society Consensus Statement on Exercise Pulmonary Hypertension

Kovacs G, Herve P, Barbera JA, Chaouat A, Chemla D, Condliffe R, Garcia G, Grunig E, **Howard L**, Humbert M, Lau E, Laveneziana P, Lewis GD, Naeije R, Peacock A, Rosenkranz S, Saggar R, Ulrich S, Vizza D, Vonk Noordegraaf A, Olschewski H. An official European Respiratory Society statement: pulmonary haemodynamics during exercise. Eur Respir J 2017: 50(5).

European Respiratory Society Consensus Statement on Exercise Rehabilitation in Pulmonary Hypertension

Grunig E, Eichstaedt C, Barbera JA, Benjamin N, Blanco I, Bossone E, Cittadini A, Coghlan G, Corris P, D'Alto M, D'Andrea A, Delcroix M, de Man F, Gaine S, Ghio S, Gibbs S, Gumbiene L, **Howard LS**, Johnson M, Jureviciene E, Kiely DG, Kovacs G, MacKenzie A, Marra AM, McCaffrey N, McCaughey P, Naeije R, Olschewski H, Pepke-Zaba J, Reis A, Santos M, Saxer S, Tulloh RM, Ulrich S, Vonk Noordegraaf A and Peacock AJ. ERS statement on exercise training and rehabilitation in patients with severe chronic pulmonary hypertension. *Eur Respir J*. 2019;53.

British Thoracic Society Guideline for Ambulatory Management of Pulmonary Embolism (Chair)

Howard L, Barden S, Condliffe R, Connolly V, Davies CWH, Donaldson J, Everett B, Free C, Horner D, Hunter L, Kaler J, Nelson-Piercy C, E OD, Patel R, Preston W, Sheares K and Campbell T. British Thoracic Society Guideline for the initial outpatient management of pulmonary embolism (PE). *Thorax*. 2018;73:ii1-ii29.

British Thoracic Society Guideline for Emergency Oxygen Therapy in Adults in conjunction with 21 other major British societies

Co-Chair (Academic) for Emergency Oxygen Guideline Update

O'Driscoll BR, **Howard LS**, Earis J, Mak V, British Thoracic Society Emergency Oxygen Guideline G, Group BTSEOGD. BTS guideline for oxygen use in adults in healthcare and emergency settings. *Thorax* 2017: 72(Suppl 1): ii1-ii90.

O'Driscoll BR, **Howard LS**, Earis J, Mak V. British Thoracic Society Guideline for oxygen use in adults in healthcare and emergency settings. *BMJ Open Respir Res* 2017: 4(1): e000170.

Co-Editor and lead for physiology sections (2008)

O'Driscoll, B. R., **Howard, L. S.** & Davison, A. G. BTS guideline for emergency oxygen use in adult patients. *Thorax*, 2008;**63 Suppl 6**;vi1-68.

National Clinical Guideline Centre, Routine preoperative tests for elective surgery

Routine preoperative tests for elective surgery, NG45, April 2016

Member of guideline development group

7th World Symposium in Pulmonary Hypertension Task Force, Barcelona 2024

Task force member – Supportive measures in Pulmonary Hypertension

Preston IR, **Howard LS**, Langleben D, Lichtblau M, Pulido T, Souza R and Olsson KM. Management of pulmonary hypertension in special conditions. *Eur Respir J*. 2024;64.

6th World Symposium in Pulmonary Hypertension Task Force, Nice 2018

McGoon MD, Ferrari P, Armstrong I, Denis M, **Howard LS**, Lowe G, Mehta S, Murakami N and Wong BA. The importance of patient perspectives in pulmonary hypertension. *Eur Respir J*. 2019;53.

5th World Symposium in Pulmonary Hypertension Task Force, Nice 2013

McLaughlin, V.V., Gaine, S.P., **Howard, L.S.**, Leuchte, H.H., Mathier, M.A., Mehta, S., Palazzini, M., Park, M.H., Tapson, V.F. & Sitbon, O. Treatment goals of pulmonary hypertension. *J Am Coll Cardiol*. 2013 Dec 24;62(25 Suppl); D73-81.

British Thoracic Society Air Travel Working Group

Member and lead for sections on venous thromboembolism and cardiac diseases

Ahmedzai, S., Balfour-Lynn, I. M., Bewick, T., Buchdahl, R., Coker, R. K., Cummin, A. R., Gradwell, D. P., **Howard, L.**, Innes, J. A., Johnson, A. O., Lim, E., Lim, W. S., McKinlay, K. P., Partridge, M. R., Popplestone, M., Pozniak, A., Robson, A., Shovlin, C. L., Shrikrishna, D., Simonds, A., Tait, P. & Thomas, M. Managing passengers with stable respiratory disease planning air travel: British Thoracic Society recommendations. *Thorax*, 2011;**66 Suppl 1**;i1-30.

European Society of Cardiology and European Respiratory Society Guidelines for Pulmonary Hypertension

Guideline reviewer

Galie, N., Hoeper, M. M., Humbert, M., Torbicki, A., Vachiery, J. L., Barbera, J. A., Beghetti, M., Corris, P., Gaine, S., Gibbs, J. S., Gomez-Sanchez, M. A., Jondeau, G., Klepetko, W., Opitz, C., Peacock, A., Rubin, L., Zellweger, M., Simonneau, G., Vahanian, A., Auricchio, A., Bax, J., Ceconi, C., Dean, V., Filippatos, G., Funck-Brentano, C., Hobbs, R., Kearney, P., McDonagh, T., McGregor, K., Popescu, B. A., Reiner, Z., Sechtem, U., Sirnes, P. A., Tendera, M., Vardas, P., Widimsky, P., Al Attar, N., Andreotti, F., Aschermann, M., Asteggiano, R., Benza, R., Berger, R., Bonnet, D., Delcroix, M., **Howard, L.**, Kitsiou, A. N., Lang, I., Maggioni, A., Nielsen-Kudsk, J. E., Park, M., Perrone-Filardi, P., Price, S., Domenech, M. T., Vonk-Noordegraaf, A. & Zamorano, J. L. Guidelines for the diagnosis and treatment of pulmonary hypertension: The Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J*, 2009;**30**;2493-537.

National Pulmonary Hypertension Service Consensus document

Member of writing group and lead for sections on Oxygen and Drug Therapies

National Pulmonary Hypertension Centres of the UK and Ireland (2008). Consensus statement on the management of pulmonary hypertension in clinical practice in the UK and Ireland. *Heart*, 2008;**94 Suppl 1**;i1-41. *Thorax*, 2008;**63 Suppl 2**;ii1-ii41.

Publications

Doctor of Philosophy

Howard, L.S.G.E. The effects of prolonged hypoxia on respiration in man. DPhil Thesis, Oxford, 1995.

Original Articles in Peer-Reviewed Journals

1-222

1. Yogeswaran A, Funderich M, Olschewski H, Kovacs G, Kiely DG, Lawrie A, Hassoun PM, Balasubramanian A, Konswa Z, Pepke-Zaba J, Cannon J, Wilkins MR, Howard L, Ghofrani HA, Grimminger F, Seeger W and Tello K. Association of pulmonary hypertension-targeted therapy and survival in precapillary pulmonary hypertension with mean pulmonary arterial pressure between 21 and 24 mmHg. *ERJ Open Res.* 2025;11.
2. Toma M, Savonitto G, Lombardi CM, Airo E, Driussi M, Gentile P, Howard L, Moschella M, Di Poi E, Pagnesi M, Monti S, Collini V, D'Angelo L, Vecchiato V, Giannoni A, Adamo M, Barbisan D, Bauleo C, Garascia A, Metra M, Sinagra G, Giudice FL, Stolfo D and Ameri P. Frequency, characteristics and risk assessment of pulmonary arterial hypertension with a left heart disease phenotype. *Clin Res Cardiol.* 2025;114:215-226.
3. Tello K, Yogeswaran A, Majeed RW, Kiely DG, Lawrie A, Brittain E, Annis JS, Olschewski H, Kovacs G, Hassoun PM, Balasubramanian A, Konswa Z, Sweatt AJ, Zamanian RT, Wilkins MR, Howard L, Arvanitaki A, Giannakoulas G, Cajigas HR, Frantz R, Williams PG, Frauendorf M, Marquardt K, Antoine T, Fuenderich M, Richter M, Grimminger F, Ghofrani HA, Wilhelm J, Seeger W and Pulmonary Vascular Research Institute GoDeep C. Association of Phosphodiesterase-5 Inhibitor Treatment With Improved Survival in Pulmonary Hypertension Associated With COPD in the Pulmonary Vascular Research Institute GoDeep Meta-Registry. *Chest.* 2025;167:224-240.
4. Suntharalingam J, Toshner MR, Blacker K, Howard LS and Kiely DG. How Can We Ensure Accessible and High-Quality Specialist Care for Patients with Pulmonary Hypertension? *Am J Respir Crit Care Med.* 2025;211:1314-1315.
5. Sivasubramaniam G, Baccelli A, Haji G, Lo Giudice F, Weaver C, Howard L and Davies R. Phenotyping vasodilator responsiveness in idiopathic pulmonary arterial hypertension: any role for the cardiopulmonary exercise test? *ERJ Open Res.* 2025;11.
6. Savonitto G, Barbisan D, Ameri P, Lombardi CM, Driussi M, Gentile P, Howard L, Toma M, Pagnesi M, Collini V, Bauleo C, Rugolotto M, Santi G, Coppi F, Pagnoni G, Bocchino PP, Raineri C, Giannoni A, Imazio M, Airo E, Metra M, Garascia A, Sinagra G, Lo Giudice F and Stolfo D. Characteristics, Prognosis, and European Society of Cardiology and European Respiratory Society Risk Stratification in Patients With Obesity and Pulmonary Arterial Hypertension. *Chest.* 2025.
7. Rothman AMK, Villar SS, Middleton J, Roussakis AA, Varian F, Zafar H, Law M, Apperley J, Bartelink IH, Said MM, Delgado-SanMartin JA, Kiely DG, Howard L, Toshner M, Wort SJ and Wilkins MR. Positioning Imatinib for Pulmonary Arterial Hypertension: A Dose-Finding Phase 2 Study. *Am J Respir Crit Care Med.* 2025;211:1018-1027.
8. Kim NH, D'Armini AM, Howard LS, Jenkins DP, Jing ZC, Mayer E, Chamitava L, Lack G, Rofael H, Solonets M and Ghofrani HA. Long-Term Safety and Efficacy of Macitentan in Inoperable Chronic Thromboembolic Pulmonary Hypertension: Results from MERIT and its Open-Label Extension. *Pulm Ther.* 2025;11:101-116.
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