

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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UNITED THERAPEUTICS CORPORATION,  
Petitioner,

v.

ACTELION PHARMACEUTICALS LTD,  
Patent Owner.

IPR2025-01139

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**PATENT OWNER ACTELION PHARMACEUTICALS LTD'S  
PRELIMINARY RESPONSE**

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| <i>Nidec Motor Corp. v Zhongshan Broad Ocean Motor Co., Ltd</i> ,<br>851 F.3d 1270 (Fed. Cir. 2017) ..... | 30, 31     |
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| <i>In re Peterson</i> ,<br>315 F.3d 1325 (Fed. Cir. 2003) .....                                           | 50         |
| <i>Rambus Inc. v. Rea</i> ,<br>731 F.3d 1248 (Fed. Cir. 2013) .....                                       | 49, 50     |
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| <i>Takeda Chem. Indus. Ltd v. Alphapharm Pty., Ltd</i> ,<br>492 F.3d 1350 (Fed. Cir. 2007) .....          | 58         |
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## **Other Authorities**

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## **Exhibit List**

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|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2001            | United Therapeutics Form 10K Annual Report for 2013, available at: <a href="https://ir.unither.com/~media/Files/U/United-Therapeutics-IR/documents/investor-resources/quarterly-reports/2013/4Q1310K.pdf">https://ir.unither.com/~media/Files/U/United-Therapeutics-IR/documents/investor-resources/quarterly-reports/2013/4Q1310K.pdf</a>                                                                                                                                                                                                                                                                                                                                          |
| 2002            | [RESERVED]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 2003            | United Therapeutics, Our History Timeline, available at: <a href="https://www.unither.com/about-us/history">https://www.unither.com/about-us/history</a>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 2004            | U.S. FDA Approves OPSYNVI® (macitentan and tadalafil) as the First and Only Once-Daily Single-Tablet Combination Therapy for Patients with Pulmonary Arterial Hypertension (PAH) (Mar. 22, 2024), available at: <a href="https://www.jnj.com/media-center/press-releases/u-s-fda-approves-opsynvi-macitentan-and-tadalafil-as-the-first-and-only-once-daily-single-tablet-combination-therapy-for-patients-with-pulmonary-arterial-hypertension-pah">https://www.jnj.com/media-center/press-releases/u-s-fda-approves-opsynvi-macitentan-and-tadalafil-as-the-first-and-only-once-daily-single-tablet-combination-therapy-for-patients-with-pulmonary-arterial-hypertension-pah</a> |
| 2005            | [RESERVED]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 2006            | Orange Book Entry for OPSUMIT®, available at: <a href="https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=001&amp;Appl_No=204410&amp;Appl_type=N">https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=001&amp;Appl_No=204410&amp;Appl_type=N</a>                                                                                                                                                                                                                                                                                                                                                                                       |
| 2007            | Orange Book Entry for OPSYNVI®, available at: <a href="https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&amp;Appl_No=218490#44288">https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&amp;Appl_No=218490#44288</a>                                                                                                                                                                                                                                                                                                                                                                                                         |
| 2008            | Clinicaltrials.gov entry for the SERAPHIN study re: OPSUMIT® (macitentan), available at: <a href="https://clinicaltrials.gov/study/NCT00660179">https://clinicaltrials.gov/study/NCT00660179</a>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 2009            | Clinicaltrials.gov entry to the A DUE study re: OPSYNVI® (macitentan/tadalafil in one dose), available at: <a href="https://clinicaltrials.gov/study/NCT03904693">https://clinicaltrials.gov/study/NCT03904693</a>                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 2010            | Canadian Pat. No. 2,659,770                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 2011            | Decision of Canadian Court in <i>Janssen, Inc. et al. v. Sandoz Canada Inc.</i> (Court File No. T-549-20), 2022 FC 715 (Fed. Ct. May 31, 2022), <i>appeal dismissed</i> , <i>Sandoz Canada Inc. v. Janssen Inc.</i> (No. A-128-22), 2023 FCA 221 (Fed. Ct. App. Nov. 9, 2023).                                                                                                                                                                                                                                                                                                                                                                                                      |

| Exhibit#      | Reference Name                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
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|               | Available at: <a href="https://decisions.fct-cf.gc.ca/fc-cf/decisions/en/521576/1/document.do">https://decisions.fct-cf.gc.ca/fc-cf/decisions/en/521576/1/document.do</a>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 2012          | Claim 1 of the CA '770 patent                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 2013          | A. Sertkaya et al., <i>Costs of Drug Development and Research and Development Intensity in the US, 2000-2018</i> , JAMA Network Open. 2024;7(6):e2415445 (June 8, 2024).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 2014          | <i>Research and Development in the Pharmaceutical Industry</i> , Congressional Budget Office (April 2021).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 2015          | OPSYNVI® (macitentan and tadalafil) Becomes the First and Only Health Canada-Approved Once Daily Fixed Dose Combination Treatment for Patients with Pulmonary Arterial Hypertension (PAH) (Oct. 15, 2021), available at: <a href="https://www.jnj.com/media-center/press-releases/opsynvi-macitentan-and-tadalafil-becomes-the-first-and-only-health-canada-approved-once-daily-fixed-dose-combination-treatment-for-patients-with-pulmonary-arterial-hypertension-pah">https://www.jnj.com/media-center/press-releases/opsynvi-macitentan-and-tadalafil-becomes-the-first-and-only-health-canada-approved-once-daily-fixed-dose-combination-treatment-for-patients-with-pulmonary-arterial-hypertension-pah</a> |
| 2016<br>[NEW] | Declaration of Dr. Luke Howard, DPhil MB BChir FRCP                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 2017<br>[NEW] | Revatio® Label                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 2018<br>[NEW] | Adcirca® Label                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 2019<br>[NEW] | Jacobs, M., <i>Mechanism of Action of Hydralzaine on Vascular Smooth Muscle</i> , BIOCHEM. PHARMACOL. 33(18): 2915-2919 (1984)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 2020<br>[NEW] | Nielsen-Kudsk, J.E. et al., <i>K<sup>+</sup> channel opening: a new drug principle in cardiovascular medicine</i> , 76 HEART 109-116 (1996)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 2021<br>[NEW] | 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<br>[NEW] | Resnick, M.S. et al., <i>Flosequinan, a vasodilator with a novel mechanism of action</i> , 102 BR. J. PHARMACOL. 974 (1991)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 2023<br>[NEW] | Stassi, D.L. et al., <i>Ethyl-substituted erythromycin derivatives produced by directed metabolic engineering</i> , 95 PROC. NATL. ACAD. SCI. USA 7305 (1998)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

| <b>Exhibit#</b> | <b>Reference Name</b>                                                                                                                                                                 |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2024<br>[NEW]   | Humbert, M. et al., <i>Treatment of Pulmonary Arterial Hypertension</i> , N. ENGL. J. MED. 351(14): 1425-1436 (Sept 2004)                                                             |
| 2025<br>[NEW]   | Schneider, M.P. et al., <i>Contrasting Actions of Endothelin ET<sub>A</sub> and ET<sub>B</sub> Receptors in Cardiovascular Disease</i> , 47 ANNU. REV. PHARMACOL. TOXICOL. 731 (2007) |
| 2026<br>[NEW]   | 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<br>[NEW]   | Rubin, L.J. et al., <i>Bosentan Therapy for Pulmonary Arterial Hypertension</i> , N. ENGL. J. MED. 346(12): 896-903 (Mar. 2002)                                                       |
| 2028<br>[NEW]   | Humbert, M. et al., <i>Combination of bosentan with epoprostenol in pulmonary arterial hypertension: BREATHE-2</i> , 24 EUR. RESPIR. J., 353 (2004)                                   |
| 2029<br>[NEW]   | 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<br>[NEW]   | Hoepfer, M. et al., <i>Combining inhaled iloprost with bosentan in patients with idiopathic pulmonary arterial hypertension</i> , 28 EUR. RESPIR. J., 691 (2006)                      |
| 2031<br>[NEW]   | 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<br>[NEW]   | 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)                  |

### **Table of Abbreviations**

| <b>Abbreviation</b> | <b>Definition</b>                                                                                                                                                                                                                                                      |
|---------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Actelion            | Actelion Pharmaceuticals Ltd                                                                                                                                                                                                                                           |
| Bolli               | WO2002/053557 (EX1004)                                                                                                                                                                                                                                                 |
| Bolli 2012          | Martin H. Bolli et al., <i>The Discovery of N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-propylsulfamide (Macitentan), an Orally Active, Potent Dual Endothelin Receptor Antagonist</i> , 55 J. MED. CHEMISTRY 7849 (2012) (EX1024) |
| cGMP                | cyclic guanosine monophosphate                                                                                                                                                                                                                                         |
| ERA                 | endothelin receptor antagonist                                                                                                                                                                                                                                         |
| ET <sub>A</sub>     | endothelin receptor type A                                                                                                                                                                                                                                             |
| ET <sub>B</sub>     | endothelin receptor type B                                                                                                                                                                                                                                             |
| ET-1                | endothelin-1                                                                                                                                                                                                                                                           |
| ED                  | erectile dysfunction                                                                                                                                                                                                                                                   |
| Hoeper              | M.M. Hoeper et al., <i>Combination Therapy with Bosentan and Sildenafil in Idiopathic Pulmonary Arterial Hypertension</i> , 24 EUR. RESPIRATORY J. 1007 (2004) (EX1009)                                                                                                |
| Iglarz              | Marc Iglarz et al., <i>Pharmacology of Macitentan, an Orally Active Tissue-Targeting Dual Endothelin Receptor Antagonist</i> , 329 J. PHARMACOLOGY & EXPERIMENTAL THERAPEUTICS 736 (2008) (EX1011)                                                                     |
| IPAH                | idiopathic PAH                                                                                                                                                                                                                                                         |
| Keyser              | WO2006/026395 (EX1005)                                                                                                                                                                                                                                                 |
| Morice              | A.H. Morice et al., <i>Letter to the Editors, Combination Therapy with Bosentan and Phosphodiesterase-5 Inhibitor in Pulmonary Arterial Hypertension</i> , 26 EUR. RESPIRATORY J. 180 (2005) (EX1010)                                                                  |
| NO                  | nitric oxide                                                                                                                                                                                                                                                           |
| PAH                 | pulmonary arterial hypertension                                                                                                                                                                                                                                        |

| <b>Abbreviation</b> | <b>Definition</b>                   |
|---------------------|-------------------------------------|
| PDE5                | phosphodiesterase 5                 |
| PH                  | pulmonary hypertension              |
| POSA                | person of ordinary skill in the art |
| the '847 patent     | U.S. Patent No. 8,268,847           |
| UT                  | United Therapeutics Corporation     |

## **I. Introduction**

Patent Owner Actelion submits this Preliminary Response to UT's Petition challenging the '847 patent. UT has not established that it has a reasonable likelihood of prevailing on its asserted anticipation or obviousness grounds.

The '847 patent is directed to novel and nonobvious therapies for treating diseases involving vasoconstriction, most notably PAH. The claims are directed to using "the compound of formula (I)," which is an ERA developed by Actelion—now known as macitentan—in combination with a PDE5 inhibitor. *See, e.g.*, EX1001, cls. 1, 6, 10.

The combination of macitentan and PDE5 inhibitors to treat diseases involving vasoconstriction is not disclosed anywhere in the prior art, and the prior art does not make the combination obvious. Instead, UT's alleged prior art would have led a POSA away from such a combination. The inventor of the '847 patent followed a path contrary to the prior art to discover the beneficial therapeutic effect, and unexpected synergy, of combination treatments using macitentan and PDE5 inhibitors, leading to the clinical development and commercialization of Actelion's OPSYNVI®.

UT has set forth the following grounds: Ground 1: Bolli (§ 102); Ground 2: Bolli and Keyser (§ 103); and Ground 3: Bolli, Hoeper, and Morice (§ 103). Pet., 16. All of them fail.

Initially, there is nothing new about UT's grounds. The Office previously concluded on multiple occasions that the combination of macitentan with PDE5 inhibitors as claimed in the '847 patent is novel and nonobvious. During a reexamination and prosecution of a continuation, four examiners and a panel of three APJs considered the same Bolli and Keyser combination UT advances and all seven found that the subject matter covered by the '847 patent claims was patentable. Over the course of those proceedings, the Office considered all four of UT's asserted references and rejected the same or substantially the same arguments UT makes here. The Office's prior findings were correct.

UT's arguments rest on a false premise, set out in the very first sentence in the Petition: that macitentan is an ET<sub>A</sub> antagonist.<sup>1</sup> Pet., 1. As the Board previously found, macitentan is a ***dual antagonist***. EX1006, 476; EX1011, 9 ("In the present study, dual antagonism of both ET<sub>A</sub> and ET<sub>B</sub> receptors by macitentan was evidenced in vitro and in isolated organs and confirmed in vivo by the increase in ET-1 plasma concentrations."). With UT's incorrect premise removed, UT's arguments fail.

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<sup>1</sup> As explained below, there are two types of endothelin receptors: type A (ET<sub>A</sub>) and type B (ET<sub>B</sub>).

For Ground 1, UT admits that Bolli does not explicitly disclose PDE5 inhibitors, but argues Bolli anticipates anyway, alleging that a POSA would have “immediately understood” that Bolli disclosed combining macitentan with a PDE5 inhibitor. Pet., 18 (citing EX1004, 18). UT’s argument rests on a single sentence in Bolli, which lists over 30 different drugs or classes of drugs, none of which are a PDE5 inhibitor, for potential combination with Bolli’s genus of compounds (not for combination with macitentan specifically). The absence of PDE5 inhibitors shows that Bolli did not contemplate the combination UT suggests, and a POSA would not have thought otherwise. UT also combines Bolli with secondary references, such as the Viagra® and Cialis® labels, thereby violating the legal standard for anticipation by going outside of a single reference to try to supply all claim limitations.

For Ground 2, Bolli in view of Keyser does not render the claims obvious for multiple reasons. First, Keyser taught away from using a dual antagonist in combination with a PDE5 inhibitor, and a POSA would have understood macitentan to be a dual antagonist. UT’s theory is that a POSA would have considered macitentan to be an ET<sub>A</sub>-specific antagonist because it allegedly has a selectivity ratio of 782, but Keyser itself classifies ERAs with selectivity ratios under 1000 as dual antagonists. UT’s theory thus fails. Second, UT’s basic argument for Ground 2 is the same one previously before the Office: Bolli

allegedly shows combining macitentan with other drugs, Keyser teaches combining ET<sub>A</sub>-specific antagonists with PDE5 inhibitors, and therefore a POSA would have combined macitentan with PDE5 inhibitors. Pet., 30-33. As explained below, the Office's prior rationale rejecting this argument is persuasive and there is no reason to reach a different result.

For Ground 3, UT proposes combining Bolli with Hoeper and Morice, but this argument is substantially the same as combining Bolli with Keyser. UT argues Hoeper reports combining bosentan and sildenafil, and Morice reports combining bosentan and tadalafil. Pet., 59; EX1009, 1; EX1010, 1. UT then asserts a POSA would have substituted bosentan with macitentan based on Bolli. Pet., 60.

However, although Keyser focused on combining ET<sub>A</sub>-selective antagonists with PDE5 inhibitors, it also discussed a study combining bosentan with sildenafil and reported that the study was terminated due to drug interaction problems. EX1005, 2, 21. Thus, Morice and Hoeper add nothing new to what Keyser disclosed. UT has not identified a plausible rationale for why the combination of these three references would have led a POSA to combine macitentan with a PDE5 inhibitor. Moreover, Hoeper and Morice were both disclosed to the Office during the supplemental examination and the Office still issued the claims.

Additionally, Grounds 2 and 3 fail because the non-obviousness of the '847 patent claims are supported by the unexpected, synergistic results reported in the

'847 patent from combining macitentan with tadalafil and from combining macitentan with sildenafil. The Federal Circuit “has consistently held that objective indicia may often be the most probative and cogent evidence of nonobviousness. Objective indicia are essential safe-guards that protect against hindsight bias.... As a result, the Board must consider all such evidence of objective indicia” when considering obviousness. *Liqwd, Inc. v. L’Oreal USA, Inc.*, 941 F.3d 1133, 1136-1137 (Fed. Cir. 2019) (internal quotations omitted). The Office previously found this evidence to be persuasive and, as discussed in more detail below, UT has not demonstrated that the Office erred. The Petition should be denied.

## **II. Background**

### **A. Treatment of PAH**

PAH is a serious condition that affects the pulmonary circulatory system, which is responsible for delivering deoxygenated blood to the lungs and returning oxygenated blood to the heart for circulation. EX2016, ¶¶30-37. The pulmonary circulatory system consists of a network of blood vessels, *e.g.*, arteries, veins, and capillaries. *Id.* PAH is caused by the narrowing or tightening of the pulmonary arteries, which increases pulmonary blood pressure and causes the heart to work harder to pump blood through the lungs. *Id.* PAH can be difficult to detect in its

early stages, and by the time it is diagnosed and treatment is started, it may have already progressed significantly. *Id.*

PAH can be treated by disrupting processes that cause blood vessels to constrict. *Id.*, ¶38. Two processes, or pathways, are most relevant here: the endothelin pathway and the NO pathway. *Id.*

The endothelin pathway is controlled by a peptide called ET-1 which is produced and secreted by endothelial cells (the cells that line the inner walls of blood vessels). *Id.*, ¶39. ET-1 is a potent vasoconstrictor, meaning it induces vasoconstriction, or the narrowing of blood vessels. *Id.* In healthy patients, circulating ET-1 levels are low. *Id.*, ¶40. Patients with PAH have elevated ET-1 levels which results in increased vasoconstriction and increased blood pressure in the pulmonary arteries. *Id.* ET-1 interacts with two endothelin receptor types: ET<sub>A</sub> and ET<sub>B</sub>. *Id.*, ¶41, 43. The ET<sub>A</sub> receptor is found on vascular smooth muscles (muscle tissue within the walls of blood vessels). *Id.* Binding of ET-1 to the ET<sub>A</sub> receptor causes vasoconstriction and abnormal growth of vascular cells, which increases pulmonary blood pressure. *Id.* In contrast, the ET<sub>B</sub> receptor has multiple functions. *Id.*, ¶42-43. Binding of ET-1 to the ET<sub>B</sub> receptor located on endothelial cells causes vasodilation (the widening of blood vessels), as well as the clearance of ET-1, both of which reduce pulmonary blood pressure. *Id.* However, binding

of ET-1 to ET<sub>B</sub> located on vascular smooth muscle cells causes vasoconstriction and abnormal vascular cell growth, similar to ET<sub>A</sub> receptors. *Id.*

ERAs have been studied as a treatment for PAH. *Id.*, ¶44. These drugs bind to one or both of the endothelin receptors which blocks the activity of ET-1, thereby inhibiting ET-1's vasoconstrictive effect. *Id.* Through this antagonistic action, ERAs can cause vasodilation in the pulmonary circulatory system, which reduces pulmonary blood pressure. *Id.*

One of the first ERAs Actelion developed, and the first approved oral therapy for the treatment of PAH, was bosentan. Bosentan is a dual, or nonselective, antagonist, meaning it binds to both ET<sub>A</sub> and ET<sub>B</sub> receptors. *Id.*, ¶45-46. Another ERA Actelion developed is macitentan. Like bosentan, macitentan is a dual antagonist. EX1011, 6; EX1024, 6-7; EX2016, ¶¶47, 58-65.

In the early- to mid-2000s, scientists at other companies were studying ERAs that selectively bind to ET<sub>A</sub> because it was thought that such drugs offered advantages over dual antagonists. EX2016, ¶48. For example, while dual antagonists block vasoconstriction from ET<sub>A</sub> receptors, they could also interfere with the beneficial actions of ET<sub>B</sub> receptors, including ET-1 clearance and ET<sub>B</sub>-stimulated vasodilation. *Id.*; EX1005, 20-21; EX2026, 405.

The NO pathway is also important in treating PAH. EX2016, ¶38. When the body releases NO, it stimulates production of cGMP, which is a potent

vasodilator that relaxes vascular smooth muscle. *Id.*, ¶49. Certain enzymes, most predominantly PDE5, break down cGMP. *Id.* Patients with PAH have reduced NO levels and increased PDE5 levels, which reduces the amount of cGMP created and increases the amount destroyed. *Id.*, ¶50. The result is more vasoconstriction, which increases pulmonary blood pressure. *Id.*

PAH can be treated using drugs that act as PDE5-inhibitors, meaning they reduce PDE5 levels and slow the breakdown of cGMP. *Id.*, ¶51. This results in increased vasodilation and reduced blood pressure. *Id.* In 2006, there were several known PDE5 inhibitors, but the only one approved for treatment of PAH was sildenafil (Revatio®). *Id.*, ¶52; EX2017. In 2009, FDA approved use of another PDE5 inhibitor, tadalafil (Adcirca®), for treatment of PAH. EX2016, ¶52; EX2018.

The endothelin pathway and NO pathway are closely related. EX2016, ¶53. ET-1 stimulates NO production through activation of ET<sub>B</sub> receptors on endothelial cells, leading to increased levels of cGMP which causes vasodilation. *Id.*; EX1005, 20. Therefore, cGMP production may be stimulated through activating both the endothelin *and* NO pathways. EX2016, ¶53.

## **B. The Discovery of the '847 Patent Inventions**

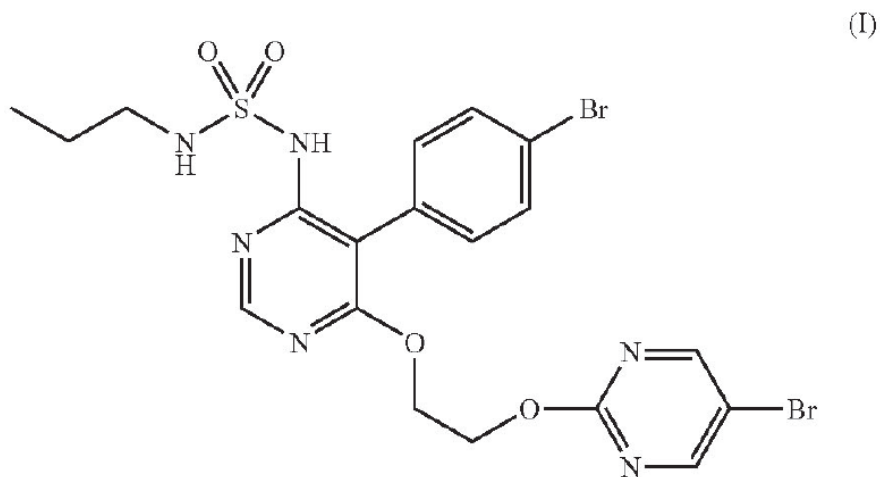
Inventor Martine Clozel and others founded Actelion in 1997. One of their focuses was on developing treatments for PAH. Through years of research, Dr.

Clozel discovered that administering a combination of two drugs—macitentan and a PDE5 inhibitor—had surprising, synergistic results in reducing the effects of PAH. EX1001, 1:60-64; 6:52-7:19. Dr. Clozel demonstrated through the use of animal models that macitentan in combination with PDE5 inhibitors tadalafil or sildenafil resulted in a decrease in blood pressure, and when administered together, the effect was surprisingly greater than the sum of the compounds administered alone. *Id.*

This invention was described in the '847 patent, which issued on September 18, 2012. EX1001. Actelion filed the first priority application for the '847 patent on August 29, 2006. UT has not disputed that the '847 patent is entitled to a priority date of August 29, 2006. Pet., 8.

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. The compound of formula (I) is macitentan. Independent claim 6 recites a pharmaceutical composition with macitentan and at least one PDE5 inhibitor, and independent claim 10 recites a method of treatment for hypertension or PH comprising administering macitentan in combination with at least one PDE5 inhibitor. 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.

### **C. OPSUMIT<sup>®</sup> and OPSYNVI<sup>®</sup>**

Over the years, Actelion has developed multiple treatments for PAH. One such treatment is OPSUMIT<sup>®</sup> (macitentan). After going through clinical trials, OPSUMIT<sup>®</sup> was approved for sale in the U.S. in 2013. EX2005. Actelion also developed a novel and nonobvious combination therapy covered by the '847 patent: administration of macitentan and a PDE5 inhibitor, such as tadalafil. After clinical trials, the combination product, OPSYNVI<sup>®</sup> (macitentan and tadalafil), was approved for sale in the U.S. in 2024. EX2006.

### **III. Level of Ordinary Skill in the Art**

For purposes of this Preliminary Response, 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 PAH. EX2016, ¶16. 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 are interested in studying drug therapy candidates. *Id.*

UT argues a POSA “would have a Ph.D. in pharmacology or a closely related field, with five years of experience in drug development for cardiovascular and/or pulmonary conditions.” Pet., 7-8. UT’s definition does not require experience treating diseases involving vasoconstriction. However, because the claims of the ’847 patent are directed to therapies for the treatment of diseases involving vasoconstriction, a POSA would be a clinician with experience treating such diseases. EX2016, ¶¶16-19.

#### **IV. Claim Construction**

UT construes various claim terms. Pet., 8-9. Solely for the purposes of this Preliminary Response, Actelion does not set forth alternative constructions because UT fails to meet its burden even under its own proposed constructions. Actelion’s silence regarding the appropriate construction of any term is not an agreement with UT’s construction (or any implicit construction). Actelion reserves the right to challenge UT’s proposed constructions, and to propose alternative or additional constructions, in any future proceedings.

For all other terms, Actelion applies their plain and ordinary meaning to a POSA, and does not believe any terms require construction for the purposes of this Preliminary Response.

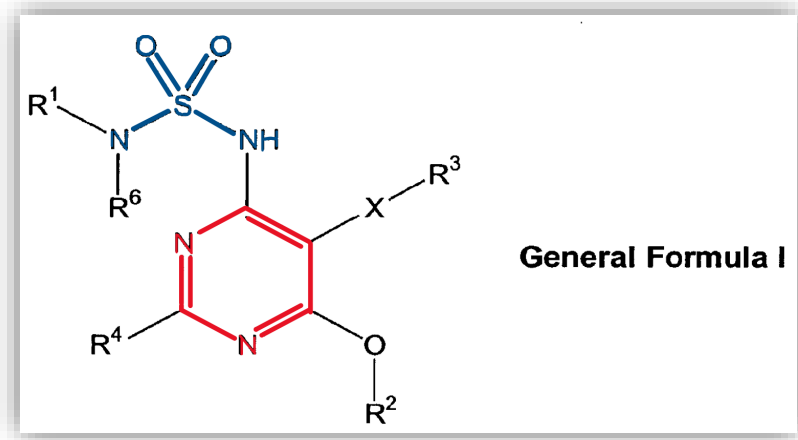
## **V. Prior Art Asserted by UT<sup>2</sup>**

### **A. Bolli**

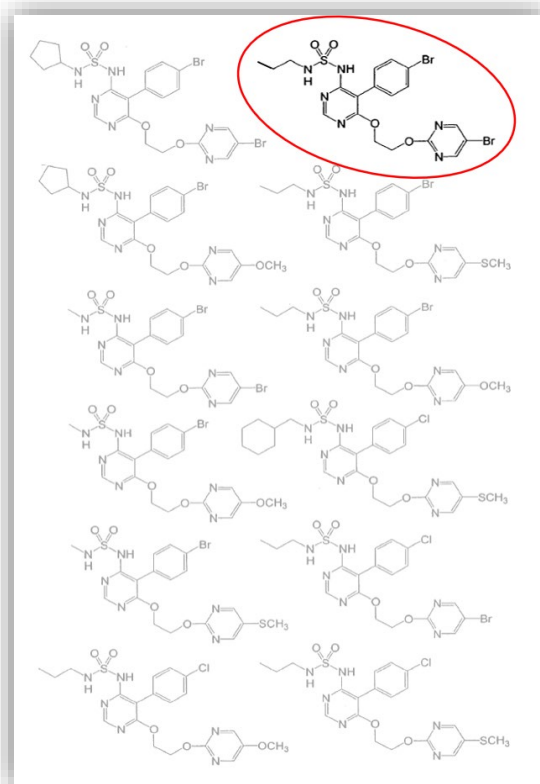
Bolli is a PCT application filed by Actelion and published in 2002. Bolli generally describes “pyrimidine-sulfamides of the general formula I and their use as active ingredients in the preparation of pharmaceutical compositions.” EX1004, 2. The described pyrimidine sulfamides contain a core pyrimidine structure (red in the annotated figure below) and an attached sulfamide group (blue), which is additionally bound to six additional categories of chemical groups or structures, indicated by X, R<sup>1</sup> through R<sup>4</sup>, and R<sup>6</sup> in the figure below. *Id.*, 13-16.

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<sup>2</sup> UT cites the Viagra<sup>®</sup>, Cialis<sup>®</sup>, and Revatio<sup>®</sup> labels as additional references. Pet., 13-14. Although it did not explicitly identify any grounds in its Petition based on these references, it uses them in combination with Bolli for certain claims in Ground 1. Pet., 19-20, 28-29.



*Id.*, 13 (annotated). Bolli goes on to identify groups of “preferred compounds” of Formula I as well as additional “preferred compounds” of Formula II-V, which vary in their X and R groups. *Id.*, 19-24. After identifying compounds of “Formula V,” Bolli discloses “[a]nother group of preferred compounds” (which appear to also be compounds of Formula V) consisting of 60 compounds, all depicted by skeletal structures without names. *Id.*, 25-29. Macitentan is one of these compounds:



*Id.*, 29 (annotated).

Bolli's disclosure of macitentan is limited only to the depiction of its structure, which appears in a list of 60 examples within a larger genus. Other than where the chemical structure is shown, macitentan is not mentioned or discussed elsewhere in Bolli, nor does Bolli express any preference for macitentan over other compounds that fall within the genus of "pyrimidine-sulfamides of the general formula I."

Bolli goes on to outline chemical reactions that may be used to prepare compounds of general formula I, and provides exemplary compounds of general formula I made through such reactions. *Id.*, 5, 30-37, 66-111. These compounds

are labeled Examples 1 through 214, and none of them are macitentan. *Id.* In fact, Examples 1-214 only include 3 of the 60 exemplary compounds provided on pages 24-28 of Bolli. *Id.*, 96 (Examples 117 and 118), 110 (Example 197). Thus, as a whole, Bolli provides nearly 250 exemplary compounds within the described genus.

Bolli further discusses compounds of general formula I and “their use as endothelin receptor antagonists,” and reports the ET<sub>A</sub>- and ET<sub>B</sub>-selective binding profiles of a subset of Examples 1-214. *Id.*, 4-9. Notably, macitentan does not appear in this list of exemplary compounds and Bolli did not report on macitentan’s binding profile.

In the Petition, UT provides a summary of Bolli that is riddled with inaccuracies. Pet., 11-12. First, UT’s statement that “Bolli describes macitentan as a preferred compound for use as an ET antagonist” is incorrect. *Id.*, 11. Bolli merely depicts macitentan in a list of 60 other compounds and as one of nearly 250 disclosed compounds in the genus. Second, UT’s conclusion that Bolli “teaches macitentan is both highly selective and potent” is inaccurate because Bolli does not provide any selectivity or potency data regarding macitentan. *Id.*, 12. Unable to cite any data specific to macitentan, UT relies on a *different* compound in Bolli, “Example 104,” which UT alleges is “nearly identical” to macitentan. Pet., 12. But Example 104 is not identical to macitentan, and Bolli does not contain any

teachings to suggest that Example 104 would exhibit the same selectivity or potency as macitentan.

Bolli does not disclose or teach the use of any PDE5 inhibitors, alone or in combination with another drug, as discussed in further detail in § VII.A.2 below.

## **B. Keyser**

Keyser is a PCT application published in March 2006. Keyser discloses “combination therapies comprising an endothelin A receptor (ET<sub>A</sub>) antagonist and a phosphodiesterase 5 (PDE5) inhibitor” to treat various disorders. EX1005, 1-2. Keyser explains that use of a “nonselective ET receptor interferes with multiple pathways whereas use of a specific ET<sub>A</sub> antagonist will act in a complementary fashion for the multiple pathways... to provide superior efficacy and/or dosage regimes and/or reduction in side effects.” *Id.*, 20. Keyser further concludes that “[n]onselective antagonists would not function as effectively” as ET<sub>A</sub>-selective antagonists. *Id.*, 21.

Keyser does not disclose macitentan. And since Keyser’s focus is entirely on the use of ET<sub>A</sub>-selective antagonists with PDE5 inhibitors, it does not teach or recommend the use of dual or “nonselective” antagonists, like macitentan, in combination with PDE5 inhibitors.

### **C. Hoeper**

Hoeper is a study published in 2004 in which nine patients with severe IPAH were treated with a combination of the “dual endothelin receptor antagonist bosentan” and sildenafil. EX1009, 1. Hoeper does not provide any data about reduction of blood pressure, but is an “observational report” showing the effects of the treatment on patients’ 6-minute walk distance. *Id.*, 3-4. The authors conclude that “combining bosentan and sildenafil *might* be feasible in patients with IPAH[,]” but the study has “several inherent limitations,” including lack of control group, small patient population, and limited observation period. *Id.*, 3 (emphasis added). Hoeper does not disclose macitentan or its use in combination with PDE5 inhibitors.

### **D. Morice**

Morice is a 2005 comment to the Hoeper article, reporting the experience of one patient treated with a combination of bosentan and sildenafil, and then a combination of bosentan and tadalafil. EX1010, 1. Morice reports that with the combination of bosentan and sildenafil, “exercise tolerance doubled,” and with the combination of bosentan and tadalafil, there was “excellent symptomatic response,” including an “estimated” measure of reduced blood pressure. *Id.* Morice does not disclose macitentan or its use in combination with PDE5 inhibitors.

## **VI. The Office Previously Considered the '847 Patent Claims and UT's Asserted Prior Art**

As explained below, the Office previously considered the validity of the claimed subject matter based on the exact art and arguments that UT raises here, and it has done so *twice*: (1) once during prosecution of U.S. Appl. No. 13/604,148 (the "'148 Application"), which is a continuation of the '847 patent, and (2) again during the supplemental examination of the '847 patent.

### **A. Original Prosecution of the '847 Patent**

During original examination of the '847 patent, the claims were rejected over Bolli in view of Keyser. *See, e.g.*, EX1002, 131-143, 218-231. Actelion pointed out that Bolli was owned by Actelion, and therefore, was not prior art under § 103(c). *Id.*, 239. The Examiner allowed the claims (*id.*, 303), and the patent issued on September 18, 2012.

### **B. Prosecution of the Continuation '148 Application**

After the '847 patent issued, Actelion prosecuted several continuations, including the '148 application. During prosecution of the '148 application, similar claims were finally rejected over Bolli and Keyser. EX1006, 114-120. The basis for the rejection was the same as UT's Ground 2 here. Bolli disclosed macitentan, taught combining it with "another active compound to treat conditions or disease which are associated with an increase in vasoconstriction," but did not disclose a PDE5 inhibitor. *Id.*, 115 (citing Bolli at 16-17). The Examiner found Keyser

taught combining an “ET antagonist and PDE5 inhibitors.” *Id.* Because Bolli taught macitentan was an ET antagonist, the Examiner concluded a POSA would have combined it with a PDE5 inhibitor per Keyser. *Id.*, 115-116. Actelion appealed.

In October 2016, the Board reversed the Examiner’s findings with respect to Bolli and Keyser. *Id.*, 458. The Board showed it fully appreciated the Examiner’s argument, summarizing the Examiner’s rationale as follows:

- Bolli disclosed macitentan as one compound with the structure of “general formula I.” EX1006, 460.
- Bolli taught “the compounds of general formula I ‘may also be used in combination with one or more other therapeutically useful substances,’ such as... vasodilators, calcium-antagonists, ACE-inhibitors, potassium activators..., ‘and other therapeutics.’”<sup>3</sup> *Id.*
- Bolli does not teach that “other therapeutics” may be PDE5 inhibitors. *Id.*, 461. That element is supplied by Keyser, which discloses combining an ET<sub>A</sub> antagonist and a PDE5 inhibitor to treat PAH. *Id.*
- Keyser discloses tadalafil and sildenafil, but not macitentan. *Id.*

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<sup>3</sup> This is the passage of Bolli that UT alleges discloses PDE5 inhibitors. Pet., 17.

- A POSA would have had reason to select macitentan as an “ET antagonist” based on Bolli and combine it with a PDE5 inhibitor based on Keyser. *Id.*, 461-62.

The Board found that the Examiner erred by rejecting the claims over Bolli and Keyser. It found Actelion submitted “persuasive evidence of unexpectedly superior results” and that this established non-obviousness. *Id.*, 463. The Board noted that administering macitentan and a PDE5 inhibitor decreased blood pressure in an amount much greater than either compound alone, thus producing a surprising and synergistic effect. *Id.*, 463 (citing ’847 patent, Examples 1-3).

The Board found that a POSA would not have expected the administration of a non-selective ET antagonist and a PDE5 inhibitor to have the synergistic effects reported in the ’847 specification. EX1006, 464. Keyser teaches that it is beneficial to combine an ET<sub>A</sub>-specific antagonist with PDE5 inhibitors, and that non-selective antagonists are not as effective because they block ET<sub>B</sub> and interfere with cGMP production. *Id.*, 465. Macitentan is a non-selective, dual ET<sub>A</sub>/ET<sub>B</sub> antagonist. *Id.*, 464. Thus, the Board concluded that a POSA most likely would have expected inferior results based on Keyser. *Id.*

Although the Board reversed the Bolli and Keyser rejection, it affirmed the rejection based on obviousness-type double patenting over the ’847 patent claims, Bolli, and Keyser. *Id.*, 466-67. The Board remanded, and after further

prosecution, the '148 application was abandoned due to its overlap with the '847 patent.

### **C. Supplemental Examination of the '847 Patent**

In September 2017, Actelion requested supplemental examination of the '847 patent. Actelion stated that Bolli was prior art under § 102(b), and that it sought to correct the exchange during original prosecution regarding Bolli not being § 103(c) art. EX1003, 3-4. In the request, Actelion presented Bolli (referred to as Bolli '557), the patent that issued from Bolli, Keyser, and another reference, Adesuyi. *Id.*, 2, 263. The request was granted, and four patent examiners considered the patent and the art during reexamination. *Id.*, 261-68.

In the first Office Action, the claims were rejected based on Bolli in view of Keyser. *Id.*, 281-82. Actelion had an interview, which was attended by all four examiners. *Id.*, 289. The parties discussed the Board's prior decision from the '148 Appeal regarding Bolli and Keyser in view of the unexpected results reported in the '847 patent. *Id.* Consistent with the arguments made during prosecution of the '148 Application, Actelion argued that a POSA would not have expected the administration of a non-selective ET antagonist such as macitentan together with a PDE5 inhibitor to have synergistic effects as reported in the '847 specification. *Id.*, 302-05.

After the interview, in January 2018, Actelion added additional dependent claims. *Id.*, 297-301. Actelion also submitted an IDS with 51 references, two of which were Hoeper and Morice. *Id.*, 354-56.

In February 2018, the Office allowed the claims, explaining:

The BOLLI references disclose the compound of formula (I), but fail to teach or fairly suggest its use in combination with a PDE5 inhibitor. KEYSER discloses the use of PDE5 inhibitors, but the PTAB has found that one of ordinary skill in the art would not have expected that, given the disclosure of KEYSER, the synergistic effect described in the disclosure of the patent under reexamination, and “...most likely would have expected inferior results...”

EX1003, 376-77. The reexamination certificate issued on April 16, 2018. *Id.*, 388.

## **VII. UT Failed To Establish a Reasonable Likelihood of Prevailing on Any Asserted Ground**

### **A. Ground 1: Bolli Does Not Anticipate the '847 Patent Claims**

All claims of the '847 patent require “at least one compound having PDE5-inhibitory properties.” EX1001, cls. 1, 6, 10. Bolli does not disclose this claim element, and thus, UT’s anticipation challenge based on Bolli fails.

Not only is UT’s anticipation challenge incorrect on the merits, it is also legally flawed and redundant in light the Office’s comprehensive prior consideration of Bolli.

#### **1. Legal Standard**

To anticipate, there must “be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of

the invention.” *Scripps Clinic & Rsch. Found. v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991), *overruled on other grounds by Abbott Labs. v. Sandoz, Inc.*, 566 F.3d 1282 (Fed. Cir. 2009). Anticipation requires a “single prior art reference” which must “disclose each and every limitation of the claimed invention, either expressly or inherently.” *SRI Int’l, Inc. v. Cisco Systems, Inc.*, 930 F.3d 1295, 1306 (Fed. Cir. 2019). An allegedly anticipating disclosure must also be “arranged” just as in the claim, rather than as “multiple, distinct teachings that the artisan might somehow combine to achieve the claimed invention.” *Microsoft Corp. v. Biscotti, Inc.*, 878 F.3d 1052, 1063, 1069 (Fed. Cir. 2017) (citation omitted). To the extent every limitation is not found in an alleged anticipatory reference, it is legal error to look to sources outside the asserted reference to attempt to “fill gaps in the reference.” *Scripps*, 927 F.2d at 1576.

## **2. Bolli Does Not Disclose a PDE5 Inhibitor**

Contrary to UT’s assertion, Bolli does not anticipate claims 1-57. Pet., 16. Every claim requires a compound having PDE5-inhibitory properties, and Bolli does not disclose any such compound. The words “phosphodiesterase type 5” or “PDE5” do not appear in Bolli, and the specific PDE5 inhibitors from the ’847 dependent claims (sildenafil, vardenafil, tadalafil, udenafil) are also absent.

UT's argument hinges on a single sentence in Bolli that uses the word "vasodilators." UT argues—incorrectly—that a POSA would readily intuit "vasodilators" to include PDE5 inhibitors. Bolli states:

*The compounds of general formula I may also be used in combination with one or more other therapeutically useful substances e.g.  $\alpha$ - and  $\beta$ -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 methyldopa, clonidine, guanabenz or reserpine and other therapeutics which serve to treat high blood pressure or any cardiac disorders.*

EX1004, 18 (emphases added).

*First*, contrary to UT's argument, a POSA would not have understood the class of drugs called "vasodilators" to include PDE5 inhibitors. EX2016, ¶¶104-115. None of the exemplary vasodilators listed in Bolli, "hydralazine, minoxidil, diazoxide or flosequinan," are PDE5 inhibitors. *Id.*, ¶¶106-111. Instead, each of them has a mechanism of action that is separate and distinct from PDE5 inhibition, which was well-known at the time. *Id.* These drugs were known to act directly on vascular smooth muscles to promote vasodilation through the inhibition of calcium release (hydralazine), through opening potassium channels (minoxidil and

diazoxide), or through interfering with the inositol phosphate signaling pathway (flosequinan). *Id.*; EX2019, 2918; EX2020, 111; EX2021, 65; EX2022, 974.

A POSA reading Bolli would not have understood “vasodilators” to include PDE5 inhibitors. *Id.*, ¶¶111-115. For example, Keyser recognizes that vasodilators and PDE5 inhibitors are different. *Id.* Keyser identifies as “drugs called vasodilators” three of the same drugs mentioned in Bolli—hydralazine, minoxidil, diazoxide—but discusses PDE5 inhibitors at length as a separate, different class of drugs. EX1005, 3-4. Thus, Nothing in Bolli or the state of the art at the time equated “vasodilators” with “PDE5 inhibitors.”

Bolli’s disclosure further points a POSA away from concluding that “vasodilators” includes *any* drug that could possibly cause vasodilation. EX2016, ¶¶112-115. Bolli’s list includes multiple classes of drugs—including  $\alpha$ - and  $\beta$ -blockers, calcium-antagonists, ACE-inhibitors, potassium activators, and angiotensin II receptor antagonists—that have the effect of vasodilation, but Bolli lists them as separate from “vasodilators.” EX1004, 18; EX2016, ¶¶112-113. That is because Bolli’s list groups classes of drugs based on their mechanism of action, not their ultimate effect. *Id.* Bolli’s choice to include separate categories for these drug classes, rather than list all of them as examples of “vasodilators,” suggests that neither Bolli nor a POSA would have considered PDE5 inhibitors to be “vasodilators” as that term is used by Bolli. *Id.*

In addition, Bolli's exclusion of certain drugs further suggests that Bolli's "vasodilators" do not include PDE5 inhibitors. For example, nitrate-based medications are closely-related to PDE5 inhibitors, and Bolli does not disclose the use of nitrate-based medications at all. EX2016, ¶114. This suggests to a POSA that when Bolli said "vasodilators," PDE5 inhibitors were not contemplated, because Bolli never mentions drugs similar to PDE5 inhibitors. *Id.*

*Second*, UT's assertion that a POSA would have made the leap from "vasodilators" to PDE5 inhibitors is impermissibly based on hindsight. UT attempts to bridge the gap in two different ways: by pointing to Bolli's mentions of ED in a different section of the document, and by arguing that because treatments for ED such as sildenafil (Viagra®) were on the market, a POSA "would have necessarily understood that Bolli's teaching of macitentan 'in combination with... vasodilators... which serve to treat high blood pressure or any cardiac disorders' disclosed combining macitentan with sildenafil and tadalafil, both of which are PDE5 inhibitors." Pet., 17-18. Both arguments fail.

Contrary to UT's assertion, Bolli's mention of ED (on page 12) in a list of more than 30 conditions that can potentially be treated by ERAs has no bearing on the meaning of the word "vasodilators" (on page 18) and would not have caused a POSA to "immediately understand" that "vasodilators" include PDE5-inhibitors. Pet., 17-18. Bolli states that the compounds of general formula I can be combined

with several classes of drugs, such as “vasodilators,” which “treat high blood pressure or any cardiac disorders.” EX1004, 18. This paragraph, which is the *only* mention of vasodilators throughout Bolli, does not mention ED. Elsewhere, Bolli states that the compounds of formula I can treat a myriad of diseases, including ED. *Id.*, 12, 17. In these paragraphs mentioning ED, there is no mention of vasodilators. Thus, Bolli does not discuss “vasodilators” in connection with ED. And while Bolli teaches that the compounds of formula I may be used to treat ED, *id.*, 12, it does not additionally teach the use of the compounds of formula I *in combination with* other types of drugs that also treat ED. Therefore, a POSA would not have understood Bolli to disclose PDE5 inhibitors merely from separate, unrelated mentions of “vasodilators” in one context and ED in a different context. EX2016, ¶¶116-121.

Based on Bolli’s mention of ED, UT argues a POSA would have thought of blockbuster PDE5 inhibitors like Viagra® (sildenafil) and Cialis® (tadalafil) and a POSA “knew” these were vasodilators. Pet., 17-18; EX1013 ¶96. UT draws exactly the wrong conclusion from Bolli. Bolli does not mention either sildenafil or tadalafil or any other PDE5 inhibitor. If a POSA would have known about sildenafil as a “blockbuster” drug as UT contends, sildenafil’s omission from Bolli was intentional and would suggest to a POSA that Bolli did not envision using sildenafil in combination with any compound of formula I. EX2016, ¶120. UT’s

reliance on tadalafil (Cialis<sup>®</sup>) is even less convincing, because it was not FDA-approved until *after* Bolli's publication, and thus was not a "commercially available treatment option[]" as UT contends. Pet., 17; EX1008, 24 ("Literature issued November, 2003").

### **3. UT's Anticipation Argument Is Legally Flawed**

In addition to failing on the facts, UT's anticipation arguments are legally flawed for at least two reasons. First, Bolli does not disclose every limitation of the claimed invention, as is required for anticipation. Second, UT's arguments misapply the law.

#### **a) No Single Reference For Anticipation**

As explained above, anticipation requires a single reference to disclose each and every limitation of the claimed invention, and it is legal error to look to secondary sources to fill in the gaps of the single reference. *SRI*, 930 F.3d at 1306; *Scripps*, 927 F.2d at 1576.

As discussed above, Bolli does not disclose PDE5 inhibitors. In an attempt to fill that gap, UT cites to art outside of Bolli to teach the use of sildenafil or tadalafil to treat ED. Pet., 18, 24-25. This combination of references is improper for anticipation.

UT's arguments with respect to the dependent claims, for example, rely heavily on the combination of Bolli with secondary references to show alleged

anticipation. For example, UT argues dependent claims 2-4, 7-9, and 11-13 (reciting specific PDE5 inhibitors including sildenafil or tadalafil) are anticipated by Bolli, but UT cites Hoeper and Morice for their disclosure of tadalafil and sildenafil (in combination with bosentan). Pet., 23. As another example, Claims 23-37 and 43-57 recite doses of macitentan and PDE5 inhibitors, but UT points to the Viagra® and Cialis® labels—despite Cialis not being approved as of Bolli’s publication (EX1008, 24)—to supply sildenafil and tadalafil, as well as doses of each agent. Pet. 28-29. Such combinations are improper for anticipation.

#### **b) UT Misapplies the Law**

UT’s anticipation argument does not apply the correct legal standard to the facts. UT argues that a “POSA would have *immediately understood, or at minimum necessarily inferred*, that Bolli disclosed macitentan combined with sildenafil and macitentan combined with tadalafil from its explicit teaching to combine macitentan with ‘vasodilators’ to treat vasoconstrictive ‘cardiac disorders’ such as ED, PH, or PAH.” Pet., 18 (emphasis added). As explained above, Bolli does not “explicitly” teach combining macitentan with any “vasodilators.” Instead, it contains one paragraph indicating that “compounds of general formula I” may be combined with a wide variety of compounds, none of which is a PDE5 inhibitor.

Regardless, UT is invoking a legal standard that does not apply in this case. UT cites *VirnetX v. Apple Inc.*, 2023 WL 6933812 (Fed. Cir. 2023), and *In re*

*Graves*, 69 F.3d 1147 (Fed. Cir. 1995), for the proposition that a POSA would have “necessarily understood” or that it would have been “immediately apparent” to combine macitentan with PDE5 inhibitors based solely on Bolli and a POSA’s supposed knowledge of sildenafil and tadalafil. Pet., 17-18.

However, the *VirnetX* line of cases makes clear that “a reference that is missing a limitation does not anticipate just because ‘a skilled artisan would at once envisage the missing limitation.’” *VirnetX*, 2023 WL 6933812, at \*4 (quoting *Nidec Motor Corp. v Zhongshan Broad Ocean Motor Co., Ltd*, 851 F.3d 1270, 1274-1275 (Fed. Cir. 2017)). As the *VirnetX* court explained: “The core inquiry is whether a person of ordinary skill in the art **would understand the reference to disclose the limitation in question**, rather than merely ‘envisage’ a limitation that is in fact missing from the reference.” *Id* (emphasis added). The *Nidec* case cited in *VirnetX* clarifies the “at once envisage” standard that UT tries to rely on here. The Federal Circuit explained:

*Kennametal* does not stand for the proposition that a reference missing a limitation can anticipate a claim if a skilled artisan viewing the reference would ‘at once envisage’ the missing limitation. Rather, *Kennametal* addresses whether the **disclosure of a limited number of combination possibilities discloses one of the possible combinations**. As we explained, the relevant question was ‘whether the number of categories and components disclosed in [the prior art reference] is so large that the combination of ruthenium and PVD coatings would not be immediately apparent to one of ordinary skill in the art.’... *Kennametal* does not permit the Board to fill in missing

limitations simply because a skilled artisan would immediately envision them.

*Nidec*, 851 F.3d at 1274-1275 (emphasis added).

Here, PDE5 inhibitors are not disclosed at all in Bolli, and therefore, they are not one of a limited number of disclosed possible combinations. UT makes the exact argument that *VirnetX*, *Nidec*, and *Kennmetal* cautioned *against*, by contending that Bolli anticipates just because a POSA would allegedly envisage the missing limitation (PDE5 inhibitors). As *VirnetX* instructs, the correct inquiry is whether a POSA would “reasonably understand or infer from [Bolli’s] teachings that every claim [limitation] was disclosed in” Bolli. *VirnetX*, 2023 WL 6933812, at \*4 (citing *Genentech, Inc. v. Hospira, Inc.*, 946 F.3d 1333, 1340–41 (Fed. Cir. 2020)). Here, as discussed above, a POSA would not have understood Bolli to teach or disclose PDE5 inhibitors, let alone macitentan in combination with PDE5 inhibitors.

The portion of *Graves* cited by UT is similarly inapposite and merely states that a prior art reference must have sufficient disclosure to allow a POSA to utilize its teachings in combination with his or her own knowledge to arrive at the claimed invention. *See Graves*, 69 F.3d at 1152 (citing *In re LeGrice*, 301 F.2d 929 (CCPA 1962)) (For a reference to anticipate, its disclosure must allow a POSA to “take its teachings in combination with his own knowledge of the particular art and be in possession of the invention.”). Bolli’s disclosure is not sufficient to anticipate

under *Graves*. A POSA would not combine Bolli's mention of "vasodilators" with her knowledge of sildenafil or tadalafil because Bolli did not point a POSA in that direction. Rather, Bolli would have pointed a POSA in an entirely different direction by identifying "vasodilators" that do not function via PDE5 inhibition, and never mentioning PDE5 inhibitors.

#### **4. Bolli Was Extensively Considered by the Office**

UT's assertion that "anticipation was not considered" with respect to Bolli during prosecution is misleading if not inaccurate. Pet., 3. Bolli was extensively considered by the Office during examination and reexamination, and the examiners necessarily would have assessed anticipation in considering Bolli. *See, e.g.*, MPEP § 2103 (instructing examiners, *inter alia*, to determine whether the claimed invention complies with § 102 by comparing the claimed subject matter to the prior art). Here, the examiners determined that Bolli did not disclose PDE5 inhibitors, and thus, did not and could not reject any of the claims based on anticipation. *See, e.g.*, EX1002, 141 ("Bolli et al. does not teach a combination with at least one compound having PDE5 inhibitory properties such as tadalafil (Applicant's elected compound)."); *id.*, 227 (same); *id.*, 305 ("The prior art does not teach the compound of formula (I) in combination with a compound that has PDE5-inhibitor [*sic*] properties. The closest art is applicant's own work (*Bolli et al. of record*), which teaches that the compound of formula (I) has ET antagonist activity and can

be used to treat conditions or diseases which are associated with an increase in vasoconstriction such as hypertension.”) (emphasis added); EX1003, 376 (“The BOLLI references disclose the compound of formula (I), but fail to teach or fairly suggest its use in combination with a PDE5 inhibitor.”).

The Office’s findings with respect to Bolli were based on the very same paragraph that UT cites in its Petition. EX1003, 267 (citing Bolli at 17 ¶3); *id.*, 281 (same). UT’s contention that the Office did not consider anticipation or this teaching from Bolli is therefore incorrect.

Bolli has also been considered by the Board, during appeal of the ’148 application, which has similar claims to the ’847 patent. In its appeal decision, the Board quoted the same paragraph that UT relies on here and found that “Bolli does not specifically teach that the ‘other therapeutics’ may be PDE5 inhibitors.” EX1006, 461.

The Office’s prior conclusion that the passage from Bolli that UT relies upon does not disclose PDE5-inhibitors was well-reasoned and persuasive. Bolli does not disclose PDE5-inhibitors and does not anticipate, so Ground 1 fails.

**B. Ground 2: The ’847 Patent Claims Are Not Obvious Over Bolli in View of Keyser**

UT argues that claims 1-57 are obvious over Bolli in view of Keyser because a POSA would have turned from Bolli’s “teachings of macitentan in combination with one or more vasodilators—which a POSA knew to include PDE5 inhibitors”

to Keyser's teachings of "ET antagonists and PDE5 inhibitors." Pet., 30-35. UT is wrong. As discussed above, Bolli's "vasodilators" does not include PDE5 inhibitors, so UT's characterization of Bolli is incorrect.. Additionally, Keyser actually teaches away from the combinations claimed in the '847 patent because it teaches the use of *ET<sub>A</sub>-selective* antagonists in combination with PDE5 inhibitors, and discourages use of dual antagonists (like macitentan). The combination of Bolli and Keyser that UT proposes has been considered numerous times by the Office, and each time the Office has found the claims to be patentable. Additionally, contrary to UT's assertions, the Board did not err in considering the unexpected results reported in the '847, which confirm the invention is nonobvious. UT's challenge here offers nothing new.

### **1. Legal Standard**

For obviousness, it is "insufficient to merely identify each element in the prior art to establish unpatentability of the combined subject matter as a whole;" rather, a party alleging obviousness "must articulate the reasons one of ordinary skill in the art would have been motivated to select the references and to combine them to render the claimed invention obvious." *Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1379 (Fed. Cir. 2006). Hindsight bias is "impermissible," and one cannot use challenged claims "as a roadmap to reconstruct the claimed invention

using disparate elements from the prior art[.]” *TQ Delta, LLC v. Cisco Sys., Inc.*, 942 F.3d 1352, 1360–61 (Fed. Cir. 2019).

Furthermore, a reference “may be said to teach away” if it would lead a POSA “in a direction divergent from the path that was taken by the [patent] applicant.” *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738 (Fed. Cir. 2013) (quoting *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1327 (Fed. Cir. 2009)). And a reference that “teaches away can preclude a determination that the reference renders a claim obvious.” *In re Mouttet*, 686 F.3d 1322, 1333 (Fed. Cir. 2012).

## **2. Keyser Teaches Away From Using Dual Antagonists, Like Macitentan, in Combination with PDE5 Inhibitors**

Keyser “relates generally to combination therapies comprising an *endothelin A receptor (ET<sub>A</sub>) antagonist* and a phosphodiesterase 5 (PDE5) inhibitor..., and methods of treating various disorders comprising *administering an ET<sub>A</sub> antagonist* and a PDE5 inhibitor.” EX1005, 1-2 (emphases added).

Keyser explains the benefits of using ET<sub>A</sub>-selective antagonists and why nonselective antagonists “would not function as effectively” with PDE5 inhibitors. *Id.*, 21. A POSA considering Keyser would have understood that Keyser *teaches away* from using a dual, or nonselective, ET<sub>A</sub> and ET<sub>B</sub> antagonist (such as macitentan) in combination with a PDE5 inhibitor. EX2016, ¶¶125-130.

Keyser first discusses the drawbacks of certain therapies in treating PAH. EX1005, 20. For example, Keyser notes that sildenafil requires high doses to achieve a therapeutic effect, and that bosentan, the only approved endothelin receptor antagonist at the time of Keyser, is a “nonselective compound that blocks both the A and the B receptors.” *Id.* Keyser further explains that “use of a nonselective ET receptor interferes with multiple pathways,” thereby discouraging use of nonselective (dual) antagonists (like bosentan). *Id.* Keyser contrasts dual antagonists with “use of a specific ET<sub>A</sub> antagonist [which] 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.” *Id.* Thus, throughout, Keyser is discussing a perceived problem presented by nonselective antagonists and offering a solution: use an ET<sub>A</sub>-specific antagonist in combination with a PDE5 inhibitor like sildenafil. Keyser goes on to explain:

ET<sub>A</sub> causes vasoconstriction, while ET<sub>B</sub> causes vasodilatation.  
***Bosentan works by blocking both ET<sub>A</sub> and ET<sub>B</sub> receptors.***  
***Sitaxsentan works by only blocking the ET<sub>A</sub> and leaving the ET<sub>B</sub> unimpaired.*** The mechanism by which ET<sub>B</sub> causes vasodilatation is through stimulating the production of nitrous [*sic*] oxide... (NO), [which] 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<sub>A</sub> 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<sub>B</sub> 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).

Keyser provides strong physiological reasons to target the ET<sub>A</sub> pathway using an ET<sub>A</sub>-selective antagonist (to increase cGMP production, which leads to vasodilation), while also using a PDE5 inhibitor to complement that function (prevent the breakdown of cGMP, which also leads to vasodilation). EX2016, ¶¶127-128. Keyser describes several “embodiments” of its invention, all of which are directed to combination therapies comprising ET<sub>A</sub>-selective antagonists and PDE5 inhibitors. EX1005, 6-9. As such, Keyser’s teachings are much more than a “mild preference” for ET<sub>A</sub>-selective antagonists, as UT contends. Pet., 2; EX2016, ¶¶138. Keyser also explicitly discourages combining a nonselective, or dual, antagonist with a PDE5 inhibitor, explaining nonselective antagonists “would not function as effectively” and using an ET<sub>A</sub>-selective antagonist is “superior.” EX1005, 20-21. Based on Keyser, a POSA would not expect a nonselective antagonist to exhibit the same efficacy as an ET<sub>A</sub>-selective antagonist when combined with a PDE5 inhibitor. EX2016, ¶¶127-130. Keyser never once refers to macitentan and, as explained in §§ II.A and VII.B.3.b), macitentan is a nonselective, dual antagonist.

### **3. A POSA Would Not Have Been Motivated to Combine Bolli and Keyser**

To try to demonstrate a motivation to combine, UT relies on Bolli's teaching of combining its compounds with "vasodilators" and Keyser's statement that "it would be beneficial to combine a PDE5 inhibitor with an ET<sub>A</sub> antagonist to provide complimentary treatment and reduce dosage amounts and/or side effects related to treatment with PDE5 inhibitors." Pet., 31-32 (citing EX1005, 11). UT's combination of Bolli and Keyser hinges on (1) defining macitentan as an ET<sub>A</sub>-selective antagonist, which it is not; and (2) showing that Bolli and Keyser pointed a POSA toward macitentan. UT fails on both counts.

#### **a) Macitentan Is a Dual Antagonist, and Would Have Been Classified As Such Under Keyser**

Macitentan is a dual, or nonselective, antagonist. *See, e.g.*, §§ II.A, VII.B.6.d). Macitentan was demonstrated to be a dual antagonist through both *in vitro* and *in vivo* studies. EX1011, 9; EX1024, 6-7; EX2016, ¶¶58-65. UT's attempts to mischaracterize macitentan as an ET<sub>A</sub>-selective antagonist are unsubstantiated. Pet., 1 (citing only the '847 patent, which does *not* identify macitentan as an ET<sub>A</sub>-selective antagonist).

To try and show that macitentan is an ET<sub>A</sub>-specific antagonist, UT cites Keyser and argues that a POSA would expect macitentan to be an ET<sub>A</sub>-selective antagonist based on the selectivity ratio of a different compound disclosed in Bolli,

Example 104. Pet., 12. But, even accepting UT's unsupported theory regarding the selectivity ratio of macitentan, macitentan would be classified as a nonselective antagonist under Keyser.

Keyser sets forth criteria for ET<sub>A</sub>-selective antagonists, explaining that “[s]elective compounds for ET<sub>A</sub> antagonists according to this invention, in general, should display a relative receptor binding ratio of at least 100, ***such as more than 1000, such as in increments of 500 greater than 1000, i.e. 1500, 2000, 2500, etc., if they are going to act at only one of the receptor subtypes, e.g. ET<sub>A</sub>.***” EX1005, 16. Keyser contrasts a nonselective antagonist, bosentan, which has a “selectivity ratio of 20” (or 53 according to Table 2), 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<sub>A</sub>-specific antagonist.” EX1005, 16-17, 19. Keyser then provides examples of both nonselective and ET<sub>A</sub>-selective antagonists. Keyser's Table 2 (below, left) lists the selectivity ratios of ERA compounds, and Table 3 (right) labels each compound as either ET<sub>A</sub>-selective or as ET<sub>A</sub>/ET<sub>B</sub> nonselective. EX1005, 19. The only compounds Keyser labels as ET<sub>A</sub>-selective antagonists have a selectivity ratio of at least 1000. EX1005, 19 (highlighted in green below).<sup>4</sup>

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<sup>4</sup> Only compounds that appear in both Tables 2 and 3 have been highlighted.

| Compound   | ET <sub>A</sub> | ET <sub>B</sub> | 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             | 590             | 454         |
| TBC-11251  | 0.43            | >4300           | 10,000      |
| ZD-1811    | 1.3*            | >2000           | 1500        |

| Compound          | Selectivity                      |
|-------------------|----------------------------------|
| ABT-627           | ET <sub>A</sub>                  |
| BMS-182874        | ET <sub>A</sub>                  |
| BMS-183884        | ET <sub>A</sub>                  |
| FR-139317         | ET <sub>A</sub>                  |
| J-104132/1-753037 | ET <sub>A</sub> /ET <sub>B</sub> |
| LU-135252         | ET <sub>A</sub> /ET <sub>B</sub> |
| Bosentan          | ET <sub>A</sub> /ET <sub>B</sub> |
| Ro-48-5695        | ET <sub>A</sub>                  |
| Ro-61-0612        | ET <sub>A</sub>                  |
| Ro-61-1790        | ET <sub>A</sub>                  |
| S-0139            | ET <sub>A</sub>                  |
| SB-209670         | ET <sub>A</sub> /ET <sub>B</sub> |
| SB-217242         | ET <sub>A</sub> /ET <sub>B</sub> |
| TAK-044           | ET <sub>A</sub> /ET <sub>B</sub> |
| TBC-11251         | ET <sub>A</sub>                  |
| ZD-1811           | ET <sub>A</sub>                  |

In contrast, compounds with selectivity ratios under 1000 (e.g., 130 or 454) are all classified as nonselective ET<sub>A</sub>/ET<sub>B</sub> antagonists. *Id.* (highlighted in blue below).

| Compound   | ET <sub>A</sub> | ET <sub>B</sub> | 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             | 590             | 454         |
| TBC-11251  | 0.43            | >4300           | 10,000      |
| ZD-1811    | 1.3*            | >2000           | 1500        |

| Compound          | Selectivity                      |
|-------------------|----------------------------------|
| ABT-627           | ET <sub>A</sub>                  |
| BMS-182874        | ET <sub>A</sub>                  |
| BMS-183884        | ET <sub>A</sub>                  |
| FR-139317         | ET <sub>A</sub>                  |
| J-104132/1-753037 | ET <sub>A</sub> /ET <sub>B</sub> |
| LU-135252         | ET <sub>A</sub> /ET <sub>B</sub> |
| Bosentan          | ET <sub>A</sub> /ET <sub>B</sub> |
| Ro-48-5695        | ET <sub>A</sub>                  |
| Ro-61-0612        | ET <sub>A</sub>                  |
| Ro-61-1790        | ET <sub>A</sub>                  |
| S-0139            | ET <sub>A</sub>                  |
| SB-209670         | ET <sub>A</sub> /ET <sub>B</sub> |
| SB-217242         | ET <sub>A</sub> /ET <sub>B</sub> |
| TAK-044           | ET <sub>A</sub> /ET <sub>B</sub> |
| TBC-11251         | ET <sub>A</sub>                  |
| ZD-1811           | ET <sub>A</sub>                  |

UT contends that macitentan is an ET<sub>A</sub>-selective antagonist because it allegedly has the same or substantially the same properties as a different compound in Bolli (compound 104), which has a selectivity ratio of 683. Pet., 54. But even if compound 104 from Bolli could be analogized to macitentan in the way UT contends (it cannot be), under UT's own argument, Keyser would have classified macitentan as a nonselective antagonist. EX2016, ¶¶132-141.

**b) The Scientific Evidence Shows that Macitentan Is a Dual Antagonist**

Not only would macitentan have been classified as a dual antagonist under Keyser, but the scientific evidence confirms it is a dual antagonist.

Iglarz explains that macitentan is a “dual ET<sub>A</sub>/ET<sub>B</sub> 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<sub>A</sub> and ET<sub>B</sub> receptors.” EX1011, 2. *In vitro* assays in Iglarz demonstrate macitentan’s binding affinity and inhibitory potency for the ET<sub>A</sub> and ET<sub>B</sub> receptors, as well as its selectivity for these two receptors compared to other receptors in the body. *Id.*, 6; EX2016, ¶¶59-63; *see also* § VII.B.6.d). Iglarz also reinforces macitentan’s “dual blockade on both ET<sub>A</sub> and ET<sub>B</sub> receptors” through *in vivo* testing. EX1011, 6; EX2016, ¶¶64-65.

Bolli 2012 reports the same *in vitro* binding assay results as Iglarz, and further explains that macitentan “is a potent inhibitor of ET<sub>A</sub> with significant affinity for the ET<sub>B</sub> receptor.” EX1024, 1, 6-7. Bolli 2012 thus refers to macitentan as a “dual endothelin receptor antagonist.” *Id.*, 1.

UT has not identified any contrary scientific evidence. Thus, all of the scientific evidence in the record confirms that macitentan is a dual antagonist.

**c) Bolli and Keyser Do Not Point a POSA  
Toward Macitentan**

UT asserts a POSA considering Keyser would have chosen macitentan from Bolli but there is no plausible rationale for doing so. Bolli merely depicts macitentan among dozens of exemplary chemical compounds, which are also only a subset of the hundreds of compounds that could fall under the genus of Formula I that is disclosed. EX1004, 13-29; § V.A. Given the number of possible compounds in Bolli, a POSA would have had no reason to pick macitentan in particular, especially since Bolli does not provide any experimental data about macitentan or its binding profile. EX2016, ¶¶82-83, 143. As such, a POSA would have no motivation to combine macitentan (or any similar compound) with any specific second compound, let alone a specific class of compounds (PDE5 inhibitors) not even disclosed in Bolli. EX2016, ¶¶143-144.

By way of example, a POSA starting with Keyser would start with the criteria for ET<sub>A</sub>-selective antagonists taught therein. EX2016, ¶145. As explained above, all of the agents that Keyser identifies as an ET<sub>A</sub>-selective antagonist have a selectivity ratio of 1000 or greater. EX1005, 19. There are three compounds in Bolli that fit Keyser's criteria for being an ET<sub>A</sub>-selective antagonist. EX1004, 5-9 (summarized in table below); EX2016, ¶¶146-147. UT provides no reason why a POSA would have selected macitentan instead of one of these three compounds.

| Compound of Example | IC50 [nM]       |                 | Selectivity Ratio<br>(ET <sub>B</sub> / ET <sub>A</sub> ) |
|---------------------|-----------------|-----------------|-----------------------------------------------------------|
|                     | ET <sub>A</sub> | ET <sub>B</sub> |                                                           |
| Example 24          | 2.2             | 2496            | 1135                                                      |
| Example 117         | 0.45            | 518             | 1151                                                      |
| Example 118         | 0.34            | 611             | 1797                                                      |

To the extent UT contends that, despite Keyser's teaching in Tables 2 and 3 that a compound needs to have a selectivity ratio of 1000 to be considered an ET<sub>A</sub>-selective antagonist, all that is needed to be an ET<sub>A</sub>-selective antagonist is a selectivity ratio of 100, Bolli discloses more than 50 exemplary compounds with a selectivity ratio of at least 100. EX1004, 5-9 (Examples 12 through 21, 23 through 34, 61, 73, 80, 100 through 119, 133, 145 through 147, 160 through 163, 184, 193 through 197, 212 through 214); EX2016, ¶¶148-149. None of these compounds are macitentan, and UT again provides no reason why a POSA would have selected macitentan instead of these compounds. In sum, a POSA starting from Keyser and turning to Bolli would not have selected macitentan.

#### **4. A POSA Could Not Combine Bolli and Keyser With a Reasonable Expectation of Success**

Even assuming a POSA would have been motivated to combine Bolli and Keyser, UT has not demonstrated a POSA would have done so with a reasonable expectation of success. Citing Example 1 of Keyser, UT argues that there would be a reasonable expectation of success at arriving at the claimed combination of macitentan and PDE5 inhibitors based on Keyser's disclosure of a

pharmacokinetics study of healthy volunteers who received a combination treatment of sitaxsentan—an ET<sub>A</sub>-selective antagonist—and sildenafil. Pet., 31; EX1013 ¶189. This argument relies on an incorrect premise that macitentan is an ET<sub>A</sub>-selective antagonist. As explained above, macitentan is a dual antagonist, not an ET<sub>A</sub>-selective antagonist as used in the examples of Keyser. Thus, a POSA would not expect that replacing sitaxsentan with macitentan in the combinations of Keyser would have similar results. EX2016, ¶¶150-151, 154.

Even assuming, *arguendo*, that a POSA would be motivated to rely on Example 1 of Keyser (which she would not have been), Example 1 does not actually convey a reasonable expectation of success, because it does not demonstrate therapeutic effects of the combination of sitaxsentan and a PDE5 inhibitor. Rather, Keyser only tested the combination in healthy patients, and established that use of sitaxsentan did not negatively impact the pharmacokinetics of sildenafil (and vice versa). EX1005, 28-30. This example says nothing about the efficacy of this combination to treat diseases involving vasoconstriction. EX2016, ¶¶152-153. The other example in Keyser (Example 2) discusses a *plan* for a study to show the therapeutic effect of sitaxsentan in combination with sildenafil in patients with PAH, connective tissue disease, or congenital heart disease, EX1005, 30-31, but does not actually provide any data. EX2016, ¶155.

Thus, the examples in Keyser, even in view of Bolli, do not convey to a POSA a reasonable expectation of success. EX2016, ¶¶152-156.

Furthermore, UT's asserted reasonable expectation of success based on Example 1 of Keyser is not tied to the claim limitations, which require a combination of *macitentan* with a PDE5 inhibitor. *Teva Pharms. USA, Inc. v. Corcept Therapeutics, Inc.*, 18 F.4th 1377, 1381 (Fed. Cir. 2021) ("The reasonable-expectation-of-success analysis must be tied to the scope of the claimed invention.").

Nothing in Keyser suggests that combining a dual antagonist with a PDE5 inhibitor would be successful. Keyser only mentions one example of a combination of a dual antagonist, bosentan, with a PDE5 inhibitor and notes that the study of this combination "was terminated due to pharmacokinetic drug interaction problems." EX1005, 21. A POSA reading Keyser therefore would not have expected success by combining another dual antagonist, like macitentan, with a PDE5 inhibitor. EX2016, ¶151. Instead that person would have expected failure. *Id.* And Bolli cannot provide the missing reasonable expectation of success because it does not disclose a PDE5 inhibitor, let alone combining one with another compound.

UT also argues that a reasonable expectation of success is provided by a POSA's knowledge "that these classes of drugs [ERAs and PDE5 inhibitors] were

effective” and “that combination therapies have at minimum the potential to provide a combined effect that exceeds their efficacy individually.” Pet., 32-33. First, UT’s assertion that “these classes of drugs” were all proven to be effective at the time of invention is unsubstantiated. Second, the mere *potential* for combination therapies to have a significant combined effect, or a POSA’s interest in trying such combinations, would not have been enough to actually result in a POSA’s reasonable expectation of success in combining macitentan and a PDE5 inhibitor. Any interest of a POSA to investigate combination therapies would have meant that those combinations were, at most, obvious to try. However, it is not enough for obviousness that a combination would have been “obvious to try.” *Gillette Co. v. S.C. Johnson & Son, Inc.*, 919 F.2d 720, 725 (Fed. Cir. 1990); *see also In re Deuel*, 51 F.3d 1552, 1559 (Fed. Cir. 1995) (“A general incentive does not make obvious a particular result...”). Furthermore, even if UT could establish that combination therapies were obvious to try, it does not mean they were obviously going to work. *See, e.g., Genzyme Corporation v. Dr. Reddy’s Laboratories*, 716 Fed. Appx. 1006, 1010-1011 (Fed. Cir. 2017) (finding that untested hypotheses in a highly unpredictable art was insufficient to form a reasonable expectation of success). For example, as discussed above, Keyser suggested that certain combinations (such as bosentan and sildenafil) may not work. EX1005, 21 (“Bosentan, a non-selective antagonist, was tested with

sildenafil, but the study was terminated due to pharmacokinetic drug interaction problems.”); *see also* 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”).

#### **5. The Combination of Bolli and Keyser Was Extensively Considered by the Office**

As described in § VI, above, the combination of Bolli and Keyser was considered during reexamination of the '847, and during the prosecution of the related '148 application. EX1003, 281-282; EX1006, 55-57, 114-119, 462-465. In fact, this combination was the primary ground at issue in both proceedings. UT's obviousness challenge based on Bolli and Keyser largely rehashes the same arguments that were set forth in prior rejections and successfully overcome by Actelion. UT has not demonstrated that the Office erred or provided a reason to deviate from the Office's prior conclusions.

#### **6. Objective Indicia Support Non-Obviousness**

The non-obviousness of the '847 patent claims is further supported by objective indicia including at least the unexpected results reported in the '847 patent. Specifically, the '847 patent reports that combinations of macitentan and PDE5 inhibitors demonstrated an “unexpected synergistic effect in the treatment of diseases wherein vasoconstriction is involved.” EX1001, 1:60-64. To show this

effect, the combinations of macitentan and sildenafil and macitentan and tadalafil were studied in hypertension rat models. EX1001, 5:15-6:51. The experiments revealed that administering macitentan in combination with sildenafil or tadalafil decreased blood pressure in an amount much greater than either compound alone, thus producing a synergistic effect. *Id.*, 6:52-7:19 (Examples 1-3). These results were unexpected in light of the prior art's (*e.g.*, Keyser's) teachings that use of a dual antagonist (like macitentan) would not function as effectively as ET<sub>A</sub>-selective antagonists in combination with a PDE5 inhibitor.

The Office credited these unexpected results in finding the subject matter of the claims patentable over Bolli and Keyser. As described in § VI.B, above, during the appeal of the '148 application, which contains the same written disclosure as the '847 patent, the Board found Actelion's evidence "persuasive" that a POSA would not have expected the synergistic effects produced by the administration of the compound of Formula (I) and a PDE5 inhibitor. EX1006, 463-465. The Board noted that the compound of Formula (I) is a dual antagonist, and that Keyser taught that nonselective inhibitors interfere with multiple pathways whereas an ET<sub>A</sub>-selective antagonist will act in complementary fashion and provide superior results. *Id.* During reexamination of the '847 patent, the Office adopted these same findings. EX1003, 375. The examiner additionally stated that a POSA considering Keyser, "most likely would have expected inferior results ...

in the use of the claimed combination.” *Id.*, 377. The Board should again find the evidence of unexpected results confirms the claims are not obvious.

In an attempt to avoid these prior findings, UT argues that three APJs and four examiners all erred. Pet., 5-6. Specifically, UT argues: (1) the unexpected results are not commensurate with the scope of the claims; (2) a POSA would have expected complementary results from a macitentan-PDE5 combination; (3) Actelion should not have relied on post-priority date references (Iglarz and Bolli 2012) to support the unexpected results reported in the patent, and (4) even if properly considered, Iglarz and Bolli 2012 do not support unexpected results. Pet., 45-58. UT is wrong on all counts.

**a) The Unexpected Results Reported in the '847 Patent Are Reasonably Commensurate With the Scope of the Claims**

UT argues the evidence of unexpected results is insufficient because it pertains to some, but not all, embodiments within the scope of the claims. Pet., 46-49. However, UT’s argument is based on the wrong legal standard.

The Federal Circuit has repeatedly held that “[o]bjective evidence of nonobviousness need only be *reasonably commensurate* with the scope of the claims.” *Rambus Inc. v. Rea*, 731 F.3d 1248, 1257 (Fed. Cir. 2013) (internal citations omitted); *In re Huai-Huang Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011). A patentee is not required to show “[o]bjective evidence... for every potential

embodiment of the claim.” *Rambus*, 731 F.3d at 1257. For example, where a claim covers multiple embodiments, showing commercial success of just one embodiment is sufficient. *See, e.g., In re Glatt Air Techniques, Inc.*, 630 F.3d 1026, 1030 (Fed. Cir. 2011) (applicant “need not sell every conceivable embodiment of the claims in order to rely upon evidence of commercial success”).

Here, the unexpected results reported in the ’847 patent are reasonably commensurate with the scope of the claims. Actelion has demonstrated unexpected results for not one, but two separate embodiments within the scope of the claims: (1) macitentan + sildenafil, and (2) macitentan + tadalafil. That is sufficient as a matter of law.

To contend otherwise, UT cites a narrow legal standard that is irrelevant here, specifically, “where there is a range disclosed in the prior art, and the claimed invention falls within that range[.]” *E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1008 (Fed. Cir. 2018); *see also In re Peterson*, 315 F.3d 1325, 1329-1330 (Fed. Cir. 2003) (considering a “a prior art reference that discloses a range encompassing a somewhat narrower claimed range”). In those scenarios, the patentee has the burden of showing that the entire overlapping range would have been nonobvious. *E.I. DuPont*, 904 F.3d at 1006-1007. Here, there is no range (and no combination of macitentan and a PDE5 inhibitor) in the prior art.

UT's reliance on *Genetics Institute* is similarly misplaced. Pet., 49. The Federal Circuit there upheld that unexpected results do not require an "absolute identity of scope." *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1308 (Fed. Cir. 2011). Rather, evidence of unexpected results should only be rejected when the evidence is "***plainly disproportionate***" to the scope of the claim. *Id.* (emphasis added). The court gave several examples where unexpected results were "plainly disproportionate" to claims which recite ranges overlapping with the prior art, or hundreds of compounds or combinations constituting a large genus, or preferred embodiments different than what is described in the patent. None of these scenarios apply here. The claims require macitentan in combination with PDE5 inhibitors, of which only a few were known at the time of invention, *e.g.*, those recited in dependent claim 2. Finally, the claims do not recite preferred embodiments not described in the patent. Evidence of unexpected results for two embodied combinations is sufficient.

**b) A POSA Would Not Have Expected Synergistic Results of Macitentan and PDE5 Inhibitors**

The unexpected results reported in the '847 patent demonstrated ***synergistic*** therapeutic effect of the combinations of macitentan with tadalafil and macitentan with sildenafil. Nothing in the prior art taught or suggested such synergy.

UT argues that a “POSA would have expected combining an endothelin antagonist and PDE5 inhibitor to have beneficial, complementary results” based on Keyser’s few mentions of “complementary” treatment. Pet., 49-50. From a POSA’s perspective, however, “complementary” is not the same as “synergistic.” EX2016, ¶165. Complementary is not a formal classification of a drug interaction; it merely means that two treatments may go well together. *Id.* Synergy requires a more than additive effect of a combination over monotherapies. *Id.*, ¶161. In other words, two treatments may be complementary without demonstrating any synergy. *Id.*, ¶¶165-166. Keyser’s statements about “complementary” treatments thus says nothing about any possible expectation of synergy. *Id.*

In addition, it was known that targeting multiple pathways or using drugs with different mechanisms of actions may either result in negative drug interactions, like bosentan and sildenafil, or result in weakening or hindering efficacy, as explained in Keyser. EX2016, ¶¶160-164; EX1005, 20-21; *see also* EX2032, 112.

Combining certain drugs with different mechanisms of actions is also by no means “a common sense way to maximize an intended therapeutic effect,” Pet., 51, especially when the prior art demonstrates that certain combinations, *e.g.*, a dual antagonist with a PDE5 inhibitor, would not be as effective. EX1005, 20 (“Use of a nonselective ET receptor interferes with multiple pathways whereas use of a

specific ET<sub>A</sub> antagonist will act in a complementary fashion for the multiple pathways”). In view of the prior art and the knowledge of a POSA, the ’847 patent’s synergistic results of the combination of macitentan and tadalafil and the combination of macitentan and sildenafil would have been unexpected. EX2016, ¶¶158-159.

UT’s suggestion that there is a potential for complementary action using multiple agents would go to whether the combination was obvious to try. However, as discussed above, obvious to try is not enough without a showing of a reasonable expectation of success, which is lacking here. *Gillette*, 919 F.2d at 725. UT’s remaining arguments all reiterate the “obvious to try” idea. For example, UT argues the “potential for synergy” is “one of the reasons that combinations are considered in drug development,” Pet., 51; however, mere potential would not be enough to actually forge a POSA’s reasonable expectation that such synergy could be achieved in the case of the combinations claimed in the ’847 patent. *See, e.g., OSI Pharmaceuticals, LLC v. Apotex Inc.*, 939 F.3d 1375, 1385 (Fed. Cir. 2019) (“hope that a potentially promising drug will treat a particular cancer is not enough to create a reasonable expectation of success in a highly unpredictable art such as this”); *see also* EX2016, ¶¶167-168.

Finally, the unexpected synergy of macitentan with PDE5 inhibitors is not merely “a latent property of what was well known,” as UT contends. Pet., 52.

None of the prior art asserted by UT demonstrates that dual antagonists like macitentan were known to exhibit a synergistic therapeutic effect in combination with PDE5 inhibitors. In fact, Keyser teaches the opposite: that a nonselective antagonist “interferes with multiple pathways” and “would not function as effectively.” EX1005, 20-21. Moreover, UT once again misapplies the law. Pet., 52 (citing *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991)). *In re Baxter* does not stand for the proposition that any therapeutic effect is a latent property of the agent, as UT argues here. Rather, the Federal Circuit held that “[m]ere recognition of latent properties *in the prior art* does not render nonobvious an otherwise known invention.” 952 F.2d at 392 (emphasis added). Critically, the prior art in *Baxter* disclosed a claimed embodiment (DEHP bag) which achieved the same result (suppressing hemolysis). *Id.* Here, UT has identified no prior art that teaches or discloses a combination of macitentan with a PDE5 inhibitor, much less one that achieves the synergistic therapeutic effect disclosed in the ’847 patent.

**c) Actelion’s Reliance on Post-Priority Evidence Is Proper**

Contrary to UT’s assertions, a patent owner is entitled to rely on post-priority date evidence to show both unexpected results and inherent properties of a compound. Iglarz and Bolli 2012 confirm that macitentan is a dual antagonist, which is an inherent property of the compound. EX1011, 6; EX1024, 5-7; *see also* EX1006, 385-86 (Office citing Iglarz and Bolli 2012 during appeal of the ’148

application). It is well-established that the “propert[ies] of a [] compound need not be fully recognized as of the filing date of the patent application to be relevant to nonobviousness[,]” and that “evidence of unexpected results may be... obtained after the patent’s filing or issue date.” *Genetics Inst.*, 655 F.3d at 1307 (citing *Knoll Pharm. Co. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004)) (“There is no requirement that an invention’s properties and advantages were fully known before the patent application was filed.... Evidence [of unexpected results] developed after the patent grant is not excluded from consideration, for understanding of the full range of an invention is not always achieved at the time of filing the patent application.”).

UT cites *Forest Labs* to argue that the unexpected results “must be unexpected by one of ordinary skill in the art at the time of [the] application.” Pet., 52 (citing *Forest Labs v. Sigmapharm Labs, LLC*, 918 F.3d 928, 937 (Fed. Cir. 2019)). In *Forest Labs*, however, the Federal Circuit held that post-priority evidence that alternative routes of administration could solve problems with cardiotoxic events was not unexpected because a POSA would not have been aware as of the priority date that cardiotoxic problems even existed. *Id.* In other words, results could not be unexpected if there was no countervailing expectation at the time of invention. *Forest Labs* is inapposite. Here, a POSA’s expectations at the time of the invention are demonstrated in Keyser, which taught that in

combinations with PDE5 inhibitors, dual antagonists are not effective compared to ET<sub>A</sub>-selective antagonists. As such, the Board appropriately relied on Keyser, and found that a POSA would have not have combined a dual antagonist with a PDE5 inhibitor, and if a POSA did, she would have expected inferior results. EX1006, 465. That a POSA was unaware of all macitentan's inherent properties prior to the priority date is immaterial. There is nothing improper about looking to Iglarz and Bolli 2012, both of which demonstrate that an inherent property of macitentan is that it is a dual antagonist.

**d) Iglarz and Bolli Support the Unexpected Results Reported in the '847 Patent**

UT argues that a POSA would not be surprised by the synergistic effects of macitentan and a PDE5 inhibitor based on the results reported in Iglarz and Bolli 2012, as well as the results in Bolli that pertain to a compound that is not macitentan. Pet., 54-55. Relying on “Keyser’s teaching that ‘in general’ the ET<sub>A</sub> antagonist should have a selectivity ratio of 100 or more [] based upon *in vitro* data,” UT narrowly focuses on *in vitro* ET<sub>A</sub>/ET<sub>B</sub> selectivity data presented in each of Iglarz, Bolli 2012, and Bolli to argue that macitentan would be an ET<sub>A</sub>-selective antagonist, and therefore a POSA would not be surprised by the synergistic effects of macitentan and PDE5 inhibitors. Pet., 53-55. Again, UT is wrong.

The data that UT cites from Iglarz and Bolli 2012 show that macitentan is a dual antagonist. As explained above, Keyser teaches that an ET<sub>A</sub>-selective

antagonist would have a selectivity ratio of **1000** or greater. EX1005, 16, 19; § VII.B.3.a). Therefore, Iglarz and Bolli 2012, reporting macitentan's selectivity ratio as less than 1000, would render macitentan a dual antagonist under Keyser. EX1011, 6; EX1024, 6. Iglarz and Bolli 2012 additionally report that macitentan is a dual antagonist, which for all of the reasons explained above a POSA would not expect to act synergistically with a PDE5 inhibitor. As such, Iglarz's and Bolli 2012's results reinforce a POSA's expectation that the combination of macitentan and PDE5 inhibitors would have inferior results.

Furthermore, UT's argument that Actelion mistakenly relied only on the *in vivo* results of Iglarz is incorrect because Iglarz reports the selectivity of macitentan from both *in vitro* and *in vivo* assays. EX1011, 6. UT focuses on only one *in vitro* assay in Iglarz—the receptor selectivity assay—and ignores the other reported data. Pet., 53-54. From the *in vitro* receptor selectivity assay, it was reported that macitentan has a selectivity ratio of 782. *Id.* The *in vitro* functional assay, which UT ignores, revealed that macitentan has an ET<sub>A</sub>/ET<sub>B</sub> selectivity ratio of 50/1 and behaves as a dual receptor antagonist. EX1011, 6; EX2016, ¶62. Actelion's scientists further screened macitentan *in vitro* using a panel of 63 radioligand binding assays, which UT also ignores, and found that at a high concentration, “macitentan did not inhibit by more than 50% the binding of any of the ligands tested,” meaning “macitentan is selective for the ET<sub>A</sub> and ET<sub>B</sub>

receptors.” EX1011, 6; EX2016, ¶¶63. UT is therefore incorrect that a “POSA would understand Iglarz’s *in vitro* data to **confirm** macitentan’s ET<sub>A</sub> selectivity.” Pet., 53-54 (emphasis in original). The three sets of *in vitro* data in Iglarz demonstrate macitentan exhibits dual activity *in vitro*. EX2016, ¶¶64. Iglarz goes on to explain that “[m]acitentan is best studied *in vivo* because this allows the study of the overall pharmacological effects of macitentan together with its metabolite.” EX1011, 6 The *in vivo* study confirmed what was already established by the *in vitro* studies: macitentan is a dual antagonist. EX2016, ¶¶64-65. UT has cited no evidence to suggest that the *in vitro* and *in vivo* tests showing macitentan is a dual antagonist were invalid.

UT further argues that a “POSA would understand that macitentan exceeded an ET<sub>A</sub>:ET<sub>B</sub> selectivity ratio of 100 based on Bolli,” citing Bolli’s results for the compound in Example 104, which is not macitentan. Pet., 54. UT contends that because Example 104 is a “homolog of macitentan differing structurally by only a single carbon atom,” and has a selectivity ratio 683 according to Bolli, a “POSA would have expected macitentan to have the same or substantially the same properties as Bolli’s Example 104.” Pet., 54; EX1013 ¶¶364-367. UT’s argument is unsubstantiated. For example, UT’s expert Dr. Shebuski cites no evidence for his opinion that a compound with a different structure than macitentan would have similar properties. And the Federal Circuit has cautioned that “generalization[s]”

about chemical structures should be “avoided.” *See, e.g., Takeda Chem. Indus. Ltd v. Alphapharm Pty., Ltd*, 492 F.3d 1350, 1361 (Fed. Cir. 2007) (citing *In re Grabiak*, 769 F.2d 731 (Fed. Cir. 1985)). It cannot be assumed that a compound with a similar structure to macitentan would have the same properties, as even slight changes in chemical structure can lead to major differences in properties. *See, e.g., EX2023*, 7309 (showing that the addition of a single methyl group (CH<sub>3</sub>) to erythromycin A can result in dramatic reduction in antibiotic activity). Thus, Bolli’s Example 104 does not provide a POSA any indication of the properties of macitentan or how it would behave in a combination with PDE5 inhibitors, and thus does not lead to any expectation of synergy. *EX2016*, ¶¶86, 141.

The Office has also previously considered Example 104 and found it irrelevant to whether synergistic effects would have been expected. During the prosecution of the related ’148 application, the Office considered whether macitentan was expected to be better than the “N-ethyl analog of the compound of formula (I) disclosed in Bolli,” (Example 104). *EX1006*, 464. On appeal, the Board disagreed with the Examiner that the “Appellant had a burden to test the effectiveness of that compound in combination with a PDE5 inhibitor” because “the combination of the N-ethyl analog and a PDE5 inhibitor does not exist in the prior art.” *Id.* (citing *In re Geiger*, 815 F.2d 686, 690 (Fed. Cir. 1987) (Newman, J. concurring)) (“It is not required that the claimed invention be compared with

subject matter that does not exist in the prior art.”). Accordingly, the presence of Example 104 in Bolli, despite how similar it may look to macitentan, provides a POSA with no expectation of synergy.

**C. Ground 3: The ’847 Patent Claims Are Not Obvious Over Hoeper, Morice, and Bolli**

UT’s arguments with respect to Ground 3 are short, conclusory, and recycle the same arguments made with respect to Grounds 1 and 2. Pet., 59-61. The Hoeper and Morice references add nothing to what is disclosed in Keyser. Ground 3 merely repackages Ground 2, and thus, suffers from the same deficiencies discussed above. Hoeper and Morice were also previously before the Office, and UT has failed to demonstrate that Hoeper and Morice qualify as prior art under pre-AIA §§ 102(a) and (b).

**1. Ground 3 Is Not Substantially Different From Ground 2, and Fails for the Same Reasons**

UT asserts this combination teaches the claims, arguing that Hoeper “teaches the use of an ET antagonist, bosentan, in combination with sildenafil,” Morice “teaches bosentan with tadalafil,” and “Bolli described macitentan as an especially preferred compound” and thus, a POSA would have substituted macitentan in for bosentan. Pet., 59. As an initial matter, Hoeper and Morice add nothing to what was disclosed in Keyser, which discusses a study combining bosentan with sildenafil. EX1005, 19. However, Keyser further reports that the study had to be

terminated due to drug interaction problems. *Id.* Thus, Morice and Hoeper add nothing new to what Keyser disclosed, and there is no reason to reach a different conclusion than with respect to Bolli and Keyser.

UT's rationale to combine fails. UT argues that a POSA "had reason to use macitentan instead of bosentan because Bolli encouraged use of macitentan (including because its homolog showed potency and ET<sub>A</sub> selectivity)." Pet., 60. But as discussed above in §§ VII.B.3 and VII.B.6, Bolli did not encourage use of macitentan, and a POSA would not have no reason to expect that a different compound (macitentan's "homolog") would exhibit the same selectivity or potency as macitentan. UT further asserts that a "POSA would have understood an ET antagonist which is more potent for ET<sub>A</sub> than ET<sub>B</sub> to be preferable because it would inhibit vasoconstriction more than vasodilation." Pet., 60 (citing EX1013 ¶¶285-286). UT and its expert provide no citation to support this position. The only document in the record that could support UT's position is Keyser, which provides that exact teaching: that it is better to "use [] a PDE5 inhibitor with an ET<sub>A</sub>-specific antagonist therapy in inhibiting and preventing" PAH. EX1005, 21. Thus, UT's rationale for modifying Hoeper and Morice is identical to its rationale for modifying Keyser, and fails for the same reasons discussed above with respect to Ground 2. EX2016, ¶¶170-173.

Even assuming there was a plausible rationale to combine Hoeper, Morice, and Bolli (which there is not), there would be no reasonable expectation of success in doing so. The case studies in Hoeper and Morice did not provide sufficient evidence to conclude that the combination of bosentan and sildenafil or bosentan and tadalafil would work in PAH patients. EX2016, ¶¶174-177. In particular, these studies were merely observational reports without any data demonstrating the efficacy of bosentan in combination with sildenafil or tadalafil to treat PAH. *Id.*; EX1009, 3; EX1010, 1. They provided no insight into whether other ERAs could similarly be combined with sildenafil or tadalafil to treat PAH. EX2016, ¶177. 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.

## **2. Hoeper and Morice Were Previously Before the Office**

Hoeper and Morice were both cited and disclosed to the Office in an IDS during the reexamination of the '847 patent. EX1003, 354-356. The references were initialed as considered, and the Office issued the reexamination certificate over them. *Id.*, 371-377; 383-385.

### **3. UT Has Not Proven That Hoeper and Morice Are Prior Art Under Pre-AIA §§ 102(a) and (b)**

UT has failed to establish that Hoeper and Morice are prior art under pre-AIA §§ 102(a) and (b). Although UT has provided copies of Hoeper and Morice that purport to show publication dates of 2004 and 2005, respectively, UT presents no evidence that Hoeper or Morice were “published in the European Respiratory Journal, indexed in a library, and available online” before the priority date of the ’847 patent, such that they are “prior art under pre-AIA §§102(a) and (b).” Pet., 14. In particular, UT has not demonstrated that either reference was “indexed or cataloged in some way [to] indicate that it [was] publicly accessible” or that “a person of ordinary skill could have reasonably found the website and then found the reference on that website[.]” *Samsung Elects. Co. v. Infobridge Pte. Ltd.*, 929 F.3d 1363, 1369 (Fed. Cir. 2019); *see also In re Hall*, 781 F.2d 897, 899 (Fed. Cir. 1986) (finding a reference was publicly accessible based on an affidavit by the director and manager of the library). UT’s proof of public accessibility is insufficient.

### **VIII. Conclusion**

Institution should be denied.

Dated: October 1, 2025

Respectfully submitted,

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## **CERTIFICATE OF COMPLIANCE**

I hereby certify that this brief complies with the type-volume limitations of 37 C.F.R. §42.24, because it contains 13,646 words (as determined by the Microsoft Word word-processing system used to prepare the brief).

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## **CERTIFICATE OF SERVICE**

I hereby certify that on this 1st day of October, 2025, copies of this Patent Owner's Preliminary Response and supporting exhibits have been served on the following counsel of record for Petitioner United Therapeutics Corporation:

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