UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

UNITED THERAPEUTICS CORPORATION,
Petitioner,

v.

ACTELION PHARMACEUTICALS LTD,
Patent Owner.

IPR2025-01139

PATENT OWNER ACTELION PHARMACEUTICALS LTD'S REQUEST FOR DISCRETIONARY DENIAL

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2002	[RESERVED]
2003	United Therapeutics, Our History Timeline, available at: https://www.unither.com/about-us/history
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: 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
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2006	Orange Book Entry for OPSUMIT®, available at: https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=001&Appl_No=204410&Appl_type=N
2007	Orange Book Entry for OPSYNVI®, available at: https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=218490#44288
2008	Clinicaltrials.gov entry for the SERAPHIN study re: OPSUMIT® (macitentan), available at: https://clinicaltrials.gov/study/NCT00660179
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2011	Decision of Canadian Court in *Janssen, Inc. et al. v. Sandoz Canada Inc.* (Court File No. T-549-20), 2022 FC 715 (Fed. Ct. May 31,

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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: 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

I. Introduction

Patent Owner Actelion Pharmaceuticals Ltd ("Actelion") respectfully requests discretionary denial of United Therapeutics Corporation's ("UT") petition.

The '847 patent is directed to a novel therapy for treating diseases involving vasoconstriction, most notably pulmonary arterial hypertension ("PAH"). PAH causes high blood pressure, particularly in the pulmonary vessels that deliver deoxygenated blood to the lungs and return oxygenated blood to the heart for circulation. PAH is a serious condition and often shortens patients' life expectancy.

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—an endothelin receptor antagonist Actelion developed called macitentan and a PDE-5 inhibitor—had surprising, synergistic results in reducing the effects of PAH. The treatment makes the effects of the disease more manageable for patients, improving their quality of life. After the invention, Actelion filed the first priority application for the '847 patent in August 2006, and a PCT application in 2007. Counterpart patents were granted by the patent offices in Canada and the European Union.

There are at least four reasons the Office should not waste its resources on UT's petition. *First*, Actelion has settled expectations based on the '847 patent's age, UT's knowledge of the patent, and Actelion's investments in clinical trials and

obtaining FDA approval for drugs that practice the patent. The '847 patent issued in September 2012, and after a supplemental examination, a reexamination certificate issued in April 2018. Thus, original claims 1-11 have been in force for almost 13 years, and claims 12-57, added during reexamination, have been in force for over seven years. Where a patent has been in force for more than six years, a patent owner typically has settled expectations. *Dabico Airport Sol'ns Inc. v. AXA Power ApS*, IPR2025-00408, Paper 21 at 2 (June 18, 2025) (informative).

Where a challenger has actual knowledge of a patent but fails to seek early review, that also can create settled expectations. *Google LLC v. Soundclear Techs. LLC*, IPR2025-00344, Paper 15 (Aug. 4, 2025) (settled expectations where Google had notice in 2019). Here, circumstances suggest that UT had actual notice of the '847 patent by at least early 2014. UT has long focused on PAH treatments, actively tracks competitors' drugs, and discussed macitentan in its 2013 annual report. At that time, the '847 patent was listed in the Orange Book for OPSUMIT® (macitentan), and thus, UT almost certainly knew about the patent by early 2014. UT's failure to seek early review weighs strongly in favor of discretionary denial.

Second, the Office previously considered all four of UT's asserted references and rejected the same or substantially the same arguments UT makes. A panel of three APJs and four examiners considered the same Bolli and Keyser combination UT advances. All seven found that the subject matter covered by the '847 patent

claims was patentable. UT's other two references, Hoeper and Morice, were cited during supplemental examination, and the patent still issued. There is no reason for three more APJs to consider the '847 patent claims over these references.

Third, UT's petition should be denied under 35 U.S.C. § 325(d) because the same art and arguments were previously considered. Although UT argues that the Office made errors in its prior consideration of the art, no such errors were made.

Finally, UT's arguments are objectively weak. Although Actelion will address the merits in detail in its Patent Owner Preliminary Response, UT's arguments have internal inconsistencies that justify discretionary denial.

II. Background on PAH and Treatments

Since it was formed,[1] one of Actelion's primary focuses has been developing treatments for PAH. The condition can be treated by disrupting various processes in the body that cause blood vessels to constrict. Two processes, or pathways, are most relevant here: the endothelin pathway and the nitric oxide ("NO") pathway.

First, with respect to the endothelin pathway, PAH can be treated with a drug that blocks endothelin receptors on cells in blood vessels. Endothelin is a polypeptide produced naturally by the body. It can cause a strong vasoconstrictive

[1] Actelion is now a wholly-owned subsidiary of Johnson & Johnson, an American company headquartered in New Jersey with facilities throughout the United States.

effect (blood vessels narrow). There are two types of endothelin receptors: type A (ET_A) and type B (ET_B). When endothelin activates ET_A receptors, it causes vasoconstriction, which increases blood pressure. In contrast, when it activates ET_B receptors, endothelin has a vasodilatory effect (vessels widen), which reduces blood pressure. In healthy patients, circulating endothelin levels are low. Patients with PAH, however, have elevated endothelin levels which results in increased vasoconstriction and increased blood pressure in pulmonary arteries.

Endothelin receptor antagonists ("ERAs") have been studied as a treatment for PAH. These drugs bind to the endothelin receptors and block endothelin, which prevents it from having a vasoconstrictive effect. One of the first ERAs Actelion developed was bosentan. Bosentan is a dual-antagonist, meaning it binds to both ET_A and ET_B receptors. Another ERA Actelion developed is macitentan. Like bosentan, macitentan is a dual-antagonist. In the early- to mid-2000s, many scientists at other companies were studying ERAs that selectively bind only to ET_A because it was thought that such drugs offered advantages over dual-antagonists.

Second, PAH can be treated through drugs that affect the NO pathway in cells. When the body releases NO, it stimulates production of a molecule called cyclic guanosine monophosphate (cGMP) that is a potent vasodilator that relaxes vascular smooth muscle (muscle tissue within the walls of blood vessels). Certain enzymes, most predominantly phosphodiesterase type 5 ("PDE5"), naturally break

down cGMP. In PAH patients, NO levels are reduced and PDE5 levels are increased, which reduces the amount of cGMP created and increases the amount destroyed. The result is more vasoconstriction, which increases blood pressure.

PAH can be treated using drugs that act as PDE5-inhibitors, meaning they reduce PDE5 levels and slow the breakdown of cGMP. This allows cGMP levels to be higher, resulting in increased vasodilation and lower blood pressure. In 2006, there were several known PDE5 inhibitors, but the only one approved for treatment of PAH was sildenafil (Revatio®). In 2009, the FDA approved use of another PDE5 inhibitor, tadalafil (Adcirca®), for treatment of PAH.

Over the years, Actelion has developed multiple treatments for PAH. One such treatment is OPSUMIT® (macitentan). After going through clinical trials and the FDA approval process, OPSUMIT® 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. As reported in the '847 patent, administration of macitentan and a PDE5 inhibitor has surprising, synergistic effects. EX1001, 6:57-62, 7:2-7. After years of clinical trials, the FDA approved the combination product, OPSYNVI® (macitentan/tadalafil), for sale in the U.S. in 2024. EX2006.

III. Settled Expectations Favor Denial of UT's IPR

A. The '847 Patent Has Been in Force for Almost 13 Years and UT's Failure to Seek Review Earlier Weighs in Favor of Denial

In assessing whether discretionary denial is appropriate, the Director may consider the "[s]ettled expectations of the parties, such as the length of time the claims have been in force." PTAB Interim Workload Management Memo ("March 26 Memo), 2-3; *see Dabico*, IPR2025-00408, Paper 21 at 3 ("in general, the longer the patent has been in force, the more settled expectations should be").

Actelion has strong settled expectations with respect to the '847 patent: Claims 1-11 (issued September 2012) have been in force almost 13 years, and Claims 12-57 (added in a supplemental examination ending in April 2018) for over 7 years. Where a patent has been in force for more than 6 years, the Office typically finds settled expectations. *E.g.*, *Kahoot! AS v. Interstellar, Inc.*, IPR2025-00696, Paper 12 (July 31, 2025) ("patent has been in force for over six years, creating strong settled expectations"); *HS Hyosung Adv. Mats. Corp. v. Kolon Indus., Inc.*, IPR2025-00662, Paper 12 (Aug. 14, 2025) (same).

B. UT Has Long Had Notice of the '847 Patent or Its Application

Another way settled expectations can arise is where a petitioner has had longstanding knowledge of a patent, but failed to seek early review. UT had notice of the '847 patent by at least early 2014, which is over 10 years ago, and failed to seek review until now, creating settled expectations. *See iRhythm Techs., Inc. v.*

Welch Allyn, Inc., IPR2025-00363, Paper 10 (June 6, 2025) (settled expectations where patent was "in force since… 2012 and Petitioner was aware of it as early as 2013"); *Google*, IPR2025-00344, Paper 15 (notice since 2019); *Nvidia Corp. v. Neural AI, LLC*, IPR2025-00606, Paper 18 (July 31, 2025).

UT was founded in 1996 with a focus on finding treatments for PAH, and it has been continuously developing drugs to treat PAH since at least 2000. EX2003. By 2009, the FDA had approved multiple UT PAH drugs. *Id.* As part of its business, UT tracks the market for PAH treatments and its competitors' drugs. EX2001, 22-24, 41 (listing competitors). UT also maintains awareness of the patent landscape. For example, UT tells investors that its success depends in part on its ability to "operate without infringing upon the proprietary rights of others in the United States and worldwide," including patent rights. EX2001, 16.

As reflected in its annual reports, UT kept close track of the market. For example, in its 2013 annual report, UT notes: "*Opsumit*. Approved in October 2013 in the United States… developed by Actelion for the treatment of PAH." EX2001, 23. UT also told investors that it competed with Actelion and OPSUMIT®. *Id.*, 23, 41 ("For the treatment of PAH, we compete with a number of approved products …, including… Opsumit® (macitentan)"). The report issued on February 25, 2014, and thus, UT had knowledge of OPSUMIT® at least by then.

UT was familiar with the Orange Book, and there can be little doubt that UT

checked it to see what patents covered OPSUMIT®. EX2001, 17 (discussing the Orange Book). The '847 patent was listed in the Orange Book for OPSUMIT® in November 2013. Thus, UT likely was aware of the patent by the time it released its annual report in February 2014. Despite knowing about the patent for more than 10 years, UT waited to file an IPR. UT's delay weighs in favor of denial.

C. Actelion Has Made Significant Investments in Developing Products that Practice the '847 Claims

Another independent way settled expectations can be shown is through "an extraordinary amount of investment, time, and resources dedicated to research, development, trials, and regulatory approval." *Amgen Inc. v. Bristol-Myers Squibb Co.*, IPR2025-00601, Paper 9 at 2 (July 24, 2025). Actelion has made substantial investments in developing, gaining regulatory approval, and commercializing both OPSUMIT® and OPSYNVI® that when administered can practice the '847 claims.

Discovering a new drug, getting regulatory approval, and commercializing it is expensive and time-consuming. EX2013, 1 (estimated mean cost of developing one drug is $172 million); EX2014, 2 (cost can be as high as $2 billion, often takes a decade or more). Actelion's investments include substantial preclinical research into macitentan to determine if the drug was promising for use in humans, and into determining whether combination therapy would be effective. For both OPSUMIT® and OPSYNVI®, Actelion designed, funded, got approval for, and ran clinical trials studying the therapies to ensure they are safe and effective in treating

PAH, including the following Phase III trials: the four-year SERAPHIN study on OPSUMIT® (macitentan), and the five-year A DUE study on OPSYNVI® (macitentan/tadalafil in one dose). EX2008; EX2009.

For both drugs, Actelion went through the long FDA approval process. OPSUMIT® was approved in October 2013, and OPSYNVI® in March 2024. EX2004; EX2005. The '847 patent was added to the Orange Book for OPSUMIT® in 2013, and for OPSYNVI® in 2024. EX2006; EX2007. Actelion also made investments in getting both drugs approved outside the U.S. *E.g.*, EX2015.

IV. The PTAB and Four Examiners Considered the Same or Substantially the Same Art and Arguments, Weighing in Favor of Denial

Another discretionary denial factor is "[w]hether the PTAB or another forum has already adjudicated the validity or patentability of the challenged patent claims." March 26 Memo, 2-3. As shown 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. The Office should not waste resources considering the same art and arguments yet again. *See Carvana, LLC v. Int'l Bus. Mach. Corp.*, IPR2025-00564, Paper 11 (July 10, 2025) (denying where grounds were "substantially similar to those already raised against the challenged patent in a prior district court proceeding").

A. UT's Asserted Art and Arguments

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

During supplemental examination of the '847 patent and during prosecution of the '148 Application, the combination of Bolli and Keyser (UT's Ground 2) was the primary ground at issue. UT's basic argument for Ground 2 is the same one previously before the Office: Bolli shows combining macitentan with other drugs, Keyser teaches combining ET_A antagonists with PDE5 inhibitors, and therefore a person of ordinary skill in the art ("POSA") would have combined macitentan with PDE5 inhibitors. Pet., 30-33. As explained more fully in the next section, three APJs and four examiners considered that argument and ***all seven*** found the claims patentable. There is no reason for the Office to have three more of its personnel consider that argument a third time.

For Ground 1, UT argues that Bolli anticipates. Although it admits Bolli does not explicitly disclose PDE5 inhibitors, UT argues combining macitentan with a PDE5 inhibitor would have been "immediately apparent" to a POSA based on one sentence of Bolli. Pet., 17 (citing EX1004, 18). The sentence states: "The compounds of general formula I may also be used in combination with one or more other therapeutically useful substances e.g.… vasodilators like hydralazine, minoxidil, diazoxide or flosequinan…; and other therapeutics which serve to treat

high blood pressure." EX1004, 18 (Bolli, p. 17). As shown below, both the Board and the examiners considered this exact passage of Bolli, and they concluded it did not teach use of a PDE5 inhibitor. EX1006, 460-61; EX1003, 214, 281.

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 giving bosentan and sildenafil to one patient, and Morice reports giving bosentan and tadalafil to one patient. Pet., 59; EX1009, 1; EX1010, 1. UT then asserts a POSA would have substituted bosentan with macitentan based on Bolli. Pet., 60. Although Keyser disclosed combining ET_A antagonists with PDE5 inhibitors, it also discussed a study combining bosentan with sildenafil, but reported that the study had to be terminated due to drug interaction problems. EX1005, [002], [068]. Thus, Morice and Hoeper add nothing new to what Keyser disclosed. Moreover, Hoeper and Morice were both disclosed to the Office during the supplemental examination and the Office still issued the claims.

B. The Office's Prior Consideration of the '847 Claims and UT's Asserted Art and Arguments

1. Original Prosecution of the '847 Patent

During original examination of the '847 patent, the claims were rejected over Bolli in view of other references. Actelion pointed out that Bolli was owned by Actelion, and therefore, was not prior art under § 103(c). The Examiner then allowed the claims. EX1002, 303. The '847 patent issued on September 18, 2012.

2. 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, 114-20. 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 ERA, the Examiner concluded a POSA would have combined it with a PDE5 inhibitor per Keyser. *Id.*, 116. Actelion appealed.

In October 2016, the Board reversed the Examiner's findings with respect to Bolli and Keyser. In its decision, 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.'"[2] *Id.*

[2] This is the passage of Bolli that UT alleges discloses PDE5 inhibitors. Pet., 17.

- Bolli does not teach that "other therapeutics" may be PDE5 inhibitors. *Id.*, 461. That element is supplied by Keyser, which discloses combining an ET_A antagonist and a PDE5 inhibitor to treat PAH. *Id.*
- Keyser discloses tadalafil and sildenafil, but not macitentan. *Id.*
- 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_A-specific antagonist with PDE5 inhibitors, and that non-selective antagonists are not as effective because they block ET_B and interfere with cGMP production. *Id.*, 465. Macitentan is a non-selective, dual ET_A/ET_B antagonist. 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 application was abandoned due to its overlap with the ’847 patent.

3. Supplemental Examination of the ’847 Patent

In September 2017, Actelion requested supplemental examination of the ’847 patent. In the request, Actelion stated that Bolli was prior art under § 102(b), and that it sought to correct the exchange during original prosecution regarding Bolli 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 the 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 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. In January 2018, 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.

C. Other Courts Have Considered Hoeper

A Canadian court previously rejected a validity challenge to nearly identical claims in Canadian Pat. No. 2,659,770, the '847 patent's counterpart (issued from the same PCT application) *See* EX2012 (comparing claim 1); EX2011. With respect to the Hoeper article, the court found there was "not… sufficient evidence to conclude that the combination of bosentan and sildenafil would work in PAH patients" let alone that macitentan and sildenafil would. EX2011, 50.

V. The Office Should Deny Under § 325(d) Because UT Has Not Shown that the Office Previously Erred

A petition may be denied under § 325(d) when a petitioner advances the same or substantially the same art or arguments previously considered by the

Office, as UT has done here. March 26 Memo, 2. The § 325(d) inquiry focuses on two factors: (1) whether the same or substantially the same art or arguments were presented to the Office; and (2) if so, whether the petitioner has shown the Office made a material error. *Advanced Bionics, LLC v. MED-EL Elektromedizinische Gmbh*, IPR2019-01469, Paper 6 at 7-11 (Feb. 13, 2020) (precedential).

Regarding factor (1), as demonstrated in § IV, above, the Board and four examiners considered the same art and the same or substantially the same arguments. Regarding factor (2), as explained below, UT has failed to demonstrate that the Office erred in a manner material to the patentability of the claims. UT alleges that the Office made four errors. Pet., 5-6. But no errors were made.

First, UT argues the Office erred because it did not consider anticipation by Bolli. Pet., 5. Although the Office did not explicitly consider anticipation, it did consider the same sentence in Bolli that UT contends teaches a PDE5 inhibitor. Pet., 17 (citing EX1004, 18 (Bolli's page 17)). The Office observed that 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,'" but found Bolli did not teach that the substance could be a PDE5 inhibitor. EX1006, 460-61 (citing Bolli at 17 (EX1004, 18)); EX1003, 281. This is not a case where the Office overlooked something or made an error.

Second, UT argues the Office legally erred because the unexpected results in the '847 specification are not commensurate with the claims, nullifying them as objective indicia of non-obviousness. Pet., 5. UT misstates the applicable law.

The Federal Circuit has repeatedly held that objective evidence "need only be '***reasonably commensurate*** with the scope of the claims.'" *Rambus Inc. v. Rea*, 731 F.3d 1248, 1257 (Fed. Cir. 2013); *In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011). A patent owner is not required to show "objective 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. *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").

The cases UT cites do not apply here. Pet., 45-46. UT's cases address claims "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). In those scenarios, the patent owner has the burden of showing that the entire overlapping range would have been non-obvious. *Id.* Here, there is no range (and no combination of macitentan and a PDE5 inhibitor) in the prior art. The objective evidence in the '847 patent shows surprising results for the combination of macitentan and sildenafil and of macitentan and tadalafil,

which are two embodiments covered by the claims. That is sufficient under the law. *Rambus*, 731 F.3d at 1257.

Third, UT argues the Office legally erred by considering post-priority references to support the "surprising" results. Pet., 5. Again, UT is wrong about the law. It is well-established that the "propert[ies] of a claimed 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… 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)). Iglarz (2008) and Bolli 2012 (2012) show that macitentan is a dual antagonist, which is an inherent property of the compound. EX1006, 385-86, 399; EX1011, 6. For the POSA's expectations at the time of invention, the Board relied on Keyser, which is prior art. EX1006, 464-65. As the Board previously found, a POSA would not have combined a dual antagonist with a PDE5 inhibitor, and if the POSA did, she would have expected inferior results. EX1006, 465.

Fourth, UT argues the Office erred by overlooking that Keyser teaches that any compound more selective than bosentan is an ET_A selective antagonist. Pet., 6. UT's characterization of Keyser is wrong. Keyser's Table 2 (below, left) lists the selectivity of ERA compounds, and Table 3 (right) labels the selectivity of each compound as either ET_A selective or as ET_A/ET_B nonselective. EX1005, 19.

Compound	ET_A	ET_B	Selectivity
ABT-627	0.034	63.3	1862
ABT-546	0.46	13,000	28,261
BMS-182874	48	>50,000	>1000
FR-139317	1.0	7300	7300
J-104132	0.034	0.1	2.9
LU-135252	1.4	184	130
PD-156707	0.17	139	818
Bosentan	6.5	343	53
Ro-61-1790	0.13	>130	1000
S-0139	1.0	1000	1000
SB-209670	0.20	18	90
SB-217242	1.1	111	101
T-0201	0.015	41	2700
TAK-044	1.3	590	454
TBC-11251	0.43	>4300	10,000
ZD-1611	1.3*	>2000	1500

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

The only compounds Keyser labels as ET_A selective antagonists have a selectivity ratio of at least 1000. EX1005, 19. Compounds with selectivity ratios under 1000 (*e.g.*, 130 or 454) are all classified as nonselective ET_A/ET_B antagonists even where their ratio is greater than bosentan's (53). UT contends that macitentan had a selectivity ratio of 683. Pet., 54. Thus, under UT's own argument, Keyser would have classified macitentan as a nonselective ET_A/ET_B antagonist.

VI. UT's Unpatentability Challenge is Weak

In assessing a discretionary denial request, the Director may consider the strength of the challenge. March 26 Memo, 2-3. Actelion will provide a more fulsome analysis in its POPR, but UT's arguments have several glaring problems.

For Ground 1, UT purports to argue that claims 1-57 are anticipated by Bolli, but for many claims, UT relies on ***a combination of multiple references***. For example, UT combines Bolli with the label for Cialis® (tadalafil) and the label for Viagra® (sildenafil). Pet., 28-29 (combining with EX1007 and EX1008). That is not anticipation, and the Board does not need to engage the merits to determine

UT's argument fails. But it must be considered if the Board institutes.

With respect to Ground 2, the focus of UT's argument is that a POSA looking at Keyser would view macitentan as a selective ET_A antagonist because macitentan had a selectivity ratio of 683. Pet., 54. But as explained in § V, Keyser labels compounds with a selectivity ratio under 1000 as nonselective ET_A/ET_B antagonists. Under UT's own rationale, Keyser would have classified macitentan as a nonselective ET_A/ET_B antagonist and not a selective ET_A antagonist.

With respect to Ground 3, UT nominally relies on Bolli, Hoeper, and Morice, but UT's reason to modify Hoeper and Morice comes from Keyser. UT asserts that a POSA would replace Hoeper's use of bosentan with macitentan, citing to its expert's statement that "The POSA would have understood an ET antagonist which is more potent for ET_A than ET_B—like macitentan—would be preferable because such an ET antagonist would inhibit vasoconstriction more than it would inhibit vasodilation." EX1013, ¶284. UT's expert provides no citation to support that position, and almost no explanation. However, his assertion is just his rephrasing of Keyser's teaching that it is better to "use [] a PDE5 inhibitor with an ET_A-specific antagonist therapy in inhibiting and preventing" PAH. EX1005, [069]. UT's Ground 3 suffers from the same fatal infirmities as its Ground 2.

VII. Conclusion

Actelion respectfully requests that the Director deny the petition.

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CERTIFICATE OF SERVICE

I hereby certify that on this 2nd day of September, 2025, copies of this Patent Owner's Request for Discretionary Denial have been served on the following counsel of record for Petitioner United Therapeutics Corporation:

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