Filed on behalf of: Sawai USA, Inc. and Sawai Pharmaceutical Co., Ltd.
By: Brian J. Sodikoff
Martin S. Masar III
KATTEN MUCHIN ROSENMAN, LLP
525 W. Monroe St.
Chicago, IL 60661
Tel.: 312-902-5200
Fax: 312-902-1061
Email: brian.sodikoff@kattenlaw.com
Email: martin.masar@kattenlaw.com

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SAWAI USA, INC. and SAWAI PHARMACEUTICAL CO., LTD.,
Petitioners,

v.

ASTELLAS PHARMA INC.,
Patent Owner

Case No. IPR__
Patent No. 6,346,532

PETITION FOR INTER PARTES REVIEW

TABLE OF CONTENTS

Page

TABLE OF AUTHORITIES

Page(s)

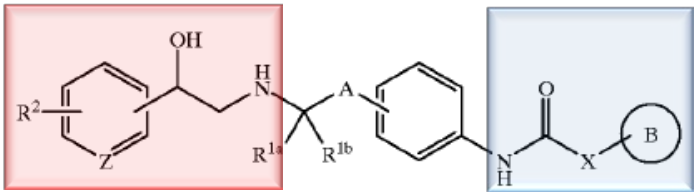
Cases

I. INTRODUCTION

Pursuant to the provisions of 35 U.S.C. § 311 and § 6 of the Leahy-Smith America Invents Act ("AIA"), and to 37 C.F.R. Part 42, Sawai USA, Inc. and Sawai Pharmaceutical Co., Ltd. ("Petitioners") hereby request review of certain claims of United States Patent No. 6,346,532 to Maruyama et al. ("the '532 patent," Ex. 1001) that issued on February 12, 2002, had an *ex parte* reexamination certificate issued on February 24, 2015, and is currently assigned to Astellas Pharma Inc. ("Patent Owner"). This Petition demonstrates, by a preponderance of the evidence, that there is a reasonable likelihood that Claims 1, 3-6, 9, 11-12, 15, and 16 of the '532 patent are obvious in light of the prior art.[1] Thus, an IPR should be instituted and these claims should be found unpatentable and ultimately canceled.

A. Brief Overview of the Challenged Claims.

The '532 patent discloses a large genus of compounds that are referred to as "amide derivatives" and have the general formula:



[1] All references to claim numbers are to those existing after the *ex parte* reexamination.

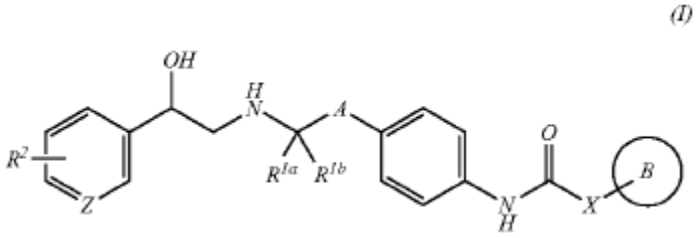
Id. at Col. 2:31-50. These compounds are phenylethanolamine derivatives (highlighted in red) connected to a variety of amide substituents (highlighted in blue) with an alkylphenyl spacer (not highlighted). The '532 patent specifically describes 113 actual examples with specific structures, but the claimed genus encompasses at least hundreds of thousands of compounds with different structural components. Ex. 1001 at Cols. 16:5-28:67; Ex. 1002 at ¶¶37-39.[2]

The '532 patent does not contain any reference to human clinical trials. The specification describes testing in two rodent models for diabetes (Ex. 1001 at Col. 11:1-55) and *in vitro* studies for β_3-receptor selectivity (*id.* at Col. 11:56-12:11), but fails to provide any actual data for any of the hundreds of thousands of compounds disclosed or claimed.

1. "Compound" claims 1, 3-6, 9, and 15 all include mirabegron.

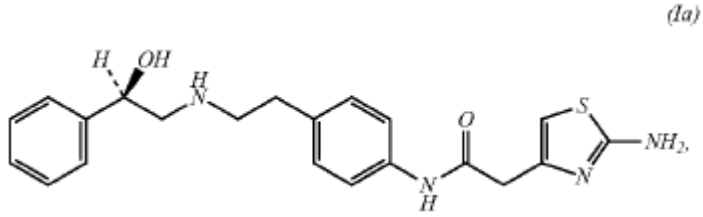
Independent Claims 1, 5, and 6, and dependent Claims 3, 4, 9, and 15 claim various sized groups of pharmaceutical compounds, each of which includes mirabegron as a species. Independent Claim 1 defines a broad genus of compounds with the following structure:

[2] Petitioners submit the declaration of Dr. Robert M. Williams, Ph.D., who is a University Distinguished Professor of Chemistry at Colorado State University and an expert in medicinal chemistry in support of this petition. Dr. Williams' relevant experience and expertise can be found in his declaration (Ex. 1002 at ¶¶1-33) and his CV (Ex. 1003).



Ex. 1001, Reexam. at Col. 1:25-35. Dependent Claims 3, 4, 9, and 15 define various subgenera of Claim 1. Ex. 1001 at Col. 46:15-17; Ex. 1001, Reexam. at Col. 2:1-23, 2:51-52; Ex. 1002 at ¶¶39-44.

Independent Claim 5 is directed specifically to mirabegron and states "[a] compound of formula (Ia):



or a salt thereof." The compound of Claim 5 is also known as (R)-2-(2-aminothiazol-4-yl)-4′-[2-(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide. Ex. 1002 at ¶42.

Independent Claim 6 defines a nine-member genus (excluding salts), one of which is mirabegron. Ex. 1001 at Col. 45:30-46:5; Ex. 1002 at ¶43. Mirabegron is also within the scope of Claims 1, 3, 4, 9, and 15. Ex. 1002 at ¶43.

These claims are unpatentable for obviousness because mirabegron, a species of them all, is obvious. *See In re Muchmore*, 433 F.2d 824, 824-25

(C.C.P.A. 1970) ("Since we agree with the board's conclusion of obviousness as to these narrow claims, the broader claims must likewise be obvious.").

2. "Composition" claims 11, 12, and 16 all include mirabegron formulated with pharmaceutically acceptable carriers.

Dependent Claims 11, 12, and 16 are directed to pharmaceutical compositions that include compounds (as defined in one of the "compound" claims), along with a pharmaceutically acceptable carrier. Compositions containing mirabegron with a pharmaceutically acceptable carrier is a species of each of these claims. These claims are unpatentable because it would be obvious to formulate mirabegron along with a pharmaceutically acceptable carrier because a POSA would have reasonably expected it to be a β3-adrenergic receptor agonist.

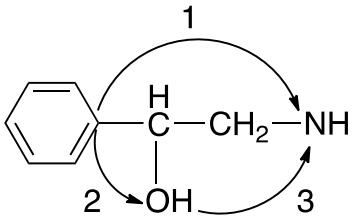
B. Brief Overview of the Relevant Technology.

The '532 patent claims priority to a Japanese Application filed on October 17, 1997. *Id.* at 1. By October 1997, adrenergic receptors (ARs) had been researched for around fifty years. In the late 1940s, two major types of ARs were designated alpha (α) and beta (β) to distinguish major differences elicited in various organ systems by adrenergic agents. *See, e.g.*, Ex. 1004 at 529. Initially, α-ARs were generally associated with contraction of smooth muscle in various organs. *See, e.g., id.* The β-AR was generally associated with inhibitory responses, except in the heart. *See, e.g., id.*

In the late 1960s, studies demonstrated that there were two β-AR subtypes. *See, e.g.*, Ex. 1004 at 529; Ex. 1005 at 2821; Ex. 1006 at 1094; Ex. 1008, at Col. 1:14-15; *see also* Ex. 1001 at Col. 1:45-50. The receptor mediating responses in the heart and lipolysis was designated β_1, while the receptor mediating vasodepressor activity and bronchodilation was labelled β_2. *See, e.g.*, Ex. 1004 at 529; Ex. 1008 at Col. 1:15-18; *see also* Ex. 1001 at Col. 1:45-50.

In the 1980s, a third subtype, β_3-AR, was hypothesized and then confirmed. *See, e.g.*, Ex. 1004 at 530; Ex. 1005 at 2821; Ex. 1006 at 1094; Ex. 1008 at Col. 1:21-24; Ex. 1025 at 168-69. As the '532 Patent admits, "it has been known … that stimulation of β_3-receptor shows an anti-obesity and an anti-hyperglycemia action (such as decrease in triglyceride, decrease in cholesterol and increase in HDL-cholesterol)." Ex. 1001 at Col. 1:45-54; *see also* Ex. 1004 at 544 (stating there was a "need for selective antagonists and labelled ligands which have sufficiently high affinity for the β_3-adrenoreceptor."). In fact, the POSA would have been motivated to look for new β_3-AR agonists because "[t]here [we]re strong indications that β_3-adrenoreceptor agonists of appropriate selectivity, efficacy and pharmacodynamics in man could prove clinically useful in the treatment of obesity in association with dieting, and for correcting raised blood sugar in diabetics." *Id.* Additional motivation to search for new β_3-AR agonists and a suggested method to do so was disclosed in Blin. *See* Ex. 1006 at 1097.

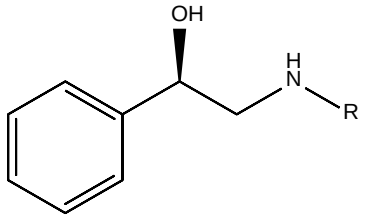
At that time, the structure-activity relationship of agonists (and antagonists) of the β_3-adrenoreceptor was also being researched and summarized. *See, e.g.*, Ex. 1006 at 1102; *see also* Ex. 1007 at PTO_00001116 (Astellas admitting Blin "discusses the structural-activity features responsible for the β_3 potency and selectivity of ligands."). In fact, Blin identified a "minimal pharmacophore" necessary for selective β_3-AR activity that included (i) an aromatic group, which could stabilize aryl-aryl interactions, (ii) a beta-hydroxyl or an ether function, which could establish a hydrogen bond, and (iii) a protonated amine, which should create an ionic bridge with a negatively charged carboxyl function inside the pocket site:



See Ex. 1006 at 1101-02, Figure 7; *see also* Ex. 1007 at PTO_00001116 (Astellas admitting "Blin teaches that potent β_3-agonists may have the following minimal pharmacophore"); PTO_00001474 (Examiner stating Blin taught that "[p]otent β_3 adrenergic receptor agonists may have one of the following [two] minimal pharmacophores …."); Ex. 1002 at ¶¶94. Blin also suggested that "β_3 efficiency is determined by the long and bulky amine substituent moiety of the ligands, which may interact with helices positioned on the opposite side, relative to those

implicated more specifically in ligand binding." Ex. 1006 at 1099, *id.* at 1103 ("extended conformations [of the long alkylamine chains], which could be adopted in the less encumbered β_3 site, may induce agonistic effects."); Ex. 1002 at ¶¶94.

It was also recognized that "[t]he stereochemistry of the phenethanolamine has a crucial influence on the potency and selectivity …" and the prior art taught methods to produce the desired R-configuration at the chiral carbon in the minimal pharmacophore:



See, e.g., Ex. 1005 at 2821; Ex. 1008 at Col. 15:13-31, Compound Ic; Col. 55, Claim 3; Ex. 1002 at ¶95.

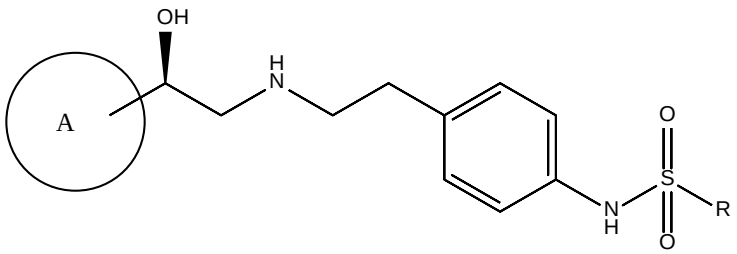
By October 1997, it was common for a research team to create a series of structurally similar compounds and to conduct testing on them, such as running them through assays.[3] *See generally* Exs. 1008-1014; *see also* Ex. 1002 at ¶96. It was also common for a pharmaceutical research team to be able to hypothesize the

[3] Notably, the specific assay used by the '532 patent Applicants to test for β_3-selectivity was disclosed in the prior art. For example, Merck US197 taught that "[r]ecently, assays have been developed which more accurately predict the effects that can be expected in humans [, which] utilize cloned human β_3 receptors which have been expressed in Chinese hamster ovary cells …." Ex. 1008 at Col. 1:59-64. "The agonist and antagonist effects of the various compounds on the cultivated cells provides an indication of the antiobesity and antidiabetic effects of the compounds in humans." *Id.* at Col. 1:64-67; Ex. 1002 at ¶96, n.5.

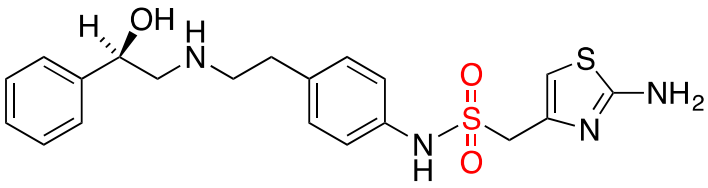
structure of compounds and to have a reasonable expectation of their pharmaceutical utility based on their similarity to other compounds. *Id.*; *see also* Ex. 1015 at PTO_00000823 (Examiner stating, "it is obvious to a chemist skilled in the art to select any species of the genus that will have reasonably similar properties and equal or better pharmaceutical use."); Ex. 1002 at ¶96. By October 1997, as admitted by Astellas, the prior art taught that compounds "that are said to be selective β_3-adrenergic receptor agonists having very little β_1 and β_2 adrenergic receptor activity" would be "expected to be useful in the treatment of Type II diabetes." Ex. 1007 at PTO_00001117 (discussing Ex. 1012); *see also* Ex. 1002 at ¶96.

The '532 patent specifically identifies the compounds disclosed in WO 95/29159 ("Merck WO159," Ex. 1013)[4] as known desirable examples of selective β3-agonists. *Id.* at Col. 1:67-2:5. Merck WO159 (and its equivalent, Merck US197) taught and disclosed phenylethanolamine derivatives that were "selective β_3 adrenergic receptor agonists with very little β_1 and β_2 adrenergic receptor activity" that had "potent activity in the treatment of Type II diabetes and obesity." Ex. 1008 at Abstract. A preferred sub-genus of Merck US197 had the following structure:

[4] This patent application shares a specification with the patent that eventually issued as U.S. Patent 5,541,197 (Ex. 1008), which is referred to herein as "Merck US197."



See, e.g., Ex. 1008 at Col. 4:25-34[5] ("[p]referred compounds of the instant invention are realized when in the above structural Formula (I): R^2 and R^3 are hydrogen …; X is $–CH_2$-; n is 0 …, m is 1; … and R^4, R^5, and R^6 are hydrogen."); Col. 15:13-31 (preferred stereoisomers); Ex. 1002 at ¶97. Even further, Merck US197 disclosed preferences for A and R that would include the following compound:



See id.; *id.* at Cols. 3:15-18; 2:41; 2:46; 3:52-53; 4:30; 15:13-31, 6:33-7:1; 15:64-16:5. This compound differs from mirabegron by the carbonyl group in mirabegron being replaced with a sulfonyl group (shown in red), which was a common biosisosteric replacement known to the POSA. Ex. 1002 at ¶¶97, 115-120, 142-156; Ex. 1007, PTO_00001475 (Examiner stating that Thornber taught that a carbonyl group may be replaced with the bioisosteric sulfone group).

[5] R in the above structure is used as a shorthand for "$(CH_2)_r$-R7."

II. STATEMENT OF PRECISE RELIEF FOR EACH CLAIM CHALLENGED

Petitioner requests review of Claims 1, 3-6, 9, 11, 12, 15 and 16 of the '532 patent under 35 U.S.C. § 311 and AIA § 6. Petitioner contends each of these Claims should be canceled as unpatentable under 35 U.S.C. § 103 (2012) as follows:

Ground	Claims	Description
1	1, 3-6, 9, 11, 12, 15, and 16	Obvious under § 103 over Merck US197 in view of Blin, in combination with Silverman (and/or Thornber), in view of a POSA's general knowledge and skill
2	1, 3-6, 9, 11, 12, 15, and 16	Obvious under §103 over Merck US197 in view of Blin, in combination with Merck US048, in further combination with Silverman (and/or Thornber), in view of a POSA's general knowledge and skill

As described above, the earliest possible priority date for the '532 patent claims is October 17, 1997. Merck US197 (Ex. 1008) issued on July 30, 1996, Blin (Ex. 1006) was published in 1993, Silverman (Ex. 1016) was published in 1992, and Thornber (Ex. 1017) was published in January 1979. Thus, each reference for Ground 1 is available as prior art against the challenged claims under 35 U.S.C. § 102(b) (2012).

As for Ground 2, Merck US048 (Ex. 1010) issued on January 4, 2000, but claims priority to a provisional application filed on January 28, 1997, and thus qualifies as prior art under, at least, 35 U.S.C. § 102(e).

III. CLAIM CONSTRUCTION

A claim subject to *inter partes* review receives the broadest reasonable construction or interpretation in light of the specification of the patent in which it appears, because among other reasons, the patent owner has an opportunity to amend the claims. *See* 37 C.F.R. § 42.100(b); *In re Cuozzo Speed Techs., LLC*, 778 F.3d 1271, 1279-82 (Fed. Cir. 2015).

The claims of the '532 patent generally use conventional terminology. Ex. 1002 at ¶84. The patent disclosure offers specific definitions (*see, e.g.*, Ex. 1001 at Cols. 3:4-4:7), but these definitions are also conventional. Ex. 1002 at ¶84. None of the challenged claims are limited to treating a certain disease state. Therefore, they are broad and cover any pharmacological utility.

Petitioners reserve the right to propose alternative constructions to any that the Patent Owner may raise during this IPR.

IV. LEVEL OF ORDINARY SKILL IN THE ART

As of October 1997, a hypothetical person having ordinary skill in the art ("POSA") would have some combination of the following skills and experience: designing target compounds towards drug discovery; designing and preparing formulations of drugs that exhibit agonistic and/or antagonistic activity; understanding the biological aspects of drug development; and understanding work

presented or published by others in the field, such as the exemplary references discussed below, representing the state of the art.

Typically, a POSA in the relevant field in October 1997 would have had a Master's or Ph.D. degree in organic, medicinal, or pharmaceutical chemistry, or a related discipline; a minimum of three years of training or experience in the pertinent field; and an appreciation for the factors relating to the drug-development process. Alternatively, a POSA might have less education but considerably more professional experience.

Also, a POSA would have knowledge of drugs for treating diabetes and/or obesity, including other β_3-adrenergic agonist compounds and/or β-adrenergic agonist compounds that have utility in treating other diseases. A POSA would also have had an understanding of pharmaceutical formulation science (as a concept and in practice) or would be part of a team with such knowledge. It would be common for a POSA to create or hypothesize a number of chemically similar compounds during drug development, with the ability to have a reasonable expectation as to their pharmacological activity based on structural similarity to other known active compounds.

The lack of specific guidance in the specification of the '532 patent confirms a high level of skill in the art. For example, the patent includes only limited description of the various pharmaceutical compositions that it claims. There are no

validated or tested dosages for those compositions and no examples describing any actual compositions produced by the inventors. Rather than providing specific guidance regarding dosages for the claimed compositions, the patent invites the POSA to turn to the knowledge and resources readily available to him/her when selecting and formulating pharmaceutical dosage forms. For instance, Applicants admitted "[a] pharmaceutical composition containing one or more of the compound [sic] of the present invention or the salt thereof as an effective ingredient is prepared using common pharmaceutically acceptable vehicles." Ex. 1001 at Col. 12:12-15. Also, rather than providing specific guidance for the compositions, the patent provides broad dosage ranges and administration methods (*id.* at Col 12: 20-29). This provides essentially no guidance for selecting actual dosages or treatment regimens. Ex. 1002 at ¶82.

Hence, the '532 patent relies on a high level of skill in the art to be able to practice the invention. Thus, the level of ordinary skill in the art as of October 17, 1997 was high.

V. DETAILED EXPLANATION OF GROUNDS FOR UNPATENTABILITY

A. [Ground 1] Claims 1, 3-6, 9, 11, 12, 15, and 16 were Obvious Under 35 U.S.C. § 103 Over Merck US197, in view of Blin, in Combination with Silverman and/or Thornber.

1. Under the Proper Legal Framework, the Obviousness Analysis Starts with the Most Structurally Similar Compound in the Prior Art.

In *Dillon*, the Federal Circuit held that

> structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness, and ... the burden (and opportunity) then falls on an applicant to rebut that prima facie case.

919 F.2d 688, 692 (Fed. Cir. 1990). Under this approach, a prior art compound qualified as a starting point for a *prima facie* case if it was structurally similar to the claimed compound and the prior art disclosed any utility regarding the prior art compound. *Id.* at 697; *see also In re Stemniski*, 444 F.2d 581, 586 (C.C.P.A. 1971). There was no requirement that the prior art compound have the same utility as the claimed compound or that the prior art compound have more beneficial properties than other prior art compounds. *See, e.g., In re Hoch*, 428 F.2d 1341 (C.C.P.A. 1970); *In re Albrecht*, 514 F.2d 1385 (C.C.P.A. 1975); *In re Wilder*, 563 F.2d 457 (C.C.P.A. 1977); *In re Wood*, 582 F.2d 638 (C.C.P.A. 1978).[6] Rather, a

[6] In some cases, the Federal Circuit has applied a strict "lead compound analysis" (LCA) to determine whether a prior art compound qualifies as a starting point to

prior art reference must be considered for everything it teaches and is not limited to the particular invention it is describing and attempting to protect. *See EWP Corp. v. Reliance Universal Inc*., 755 F.2d 898, 907 (Fed. Cir. 1985).

In *KSR Int'l v. Teleflex Inc*., the Supreme Court confirmed that obviousness determinations require an expansive, flexible, and functional approach. *See* 550 U.S. 398, 415, 419 (2007). When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a POSA has a good reason to pursue the options known in the art. *Id.* If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. *Id*. at 421. Obviousness is "necessarily a reconstruction based upon hindsight reasoning," but so long as it is based on the knowledge and content of the art rather than on the patent disclosure, that is permissible. *In re McLaughlin*, 443 F.2d 1392, 1395 (C.C.P.A. 1971).

Under *KSR* and *Dillon*, the chosen prior art compound can be any compound that has utility, and the motivation to modify it could be to make another compound with similar utility. Obviousness does not require a POSA to have the motivation of the inventors, but instead can have any motivation. A compound with a known utility can motivate a POSA to make another compound with the same utility.

---

prove obviousness. However, this is contrary to its own earlier *en banc* decision in *Dillon* and Supreme Court precedent.

Strict application of the LCA effectively restricts the knowledge of the POSA in contravention to the Patent Act, as well as Supreme Court precedent and *Dillon*. The POSA is presumed to be aware of ***all*** of the art that has come before the alleged invention. *See, e.g.*, *Mast Foos, & Co. v. Stover Mfg. Co.*, 177 U.S. 485, 493 (1900) ("Having all these various devices before him, and whatever the facts may have been, he is chargeable with a knowledge of all preexisting devices …."). Thus, the effect of a compound being disclosed in the prior art is to anticipate and hence to render unpatentable any later attempt to claim that compound. The disclosed compound also makes unpatentable any compounds that are obvious variants. *See Graham*, 383 U.S. at 14 ("An invention which has been made, and which is new in the sense that the same thing has not been made before, may still not be patentable if the difference between the new thing and what was known before is not considered sufficiently great to warrant a patent.").

By imposing a strict threshold "lead compound" requirement in some cases, the Federal Circuit has improperly constricted the concept of obviousness. For example, it was common and ordinary course for a POSA to make multiple alterations to various prior art compounds. In such situations, a new chemical compound may be obvious (or at least obvious to try) even if it is not created through alteration of the most promising compound(s) in a specific prior art field. *See KSR*, 550 U.S. at 421 ("When there is a design need or market pressure to

solve a problem and there are a finite number of identified, predictable solutions, a [POSA] has good reason to pursue the known options within his or her technical grasp."). The LCA departs from Section 103 because it fails to allow for the fact that variants of compounds disclosed in the prior art may be obvious, rather than being limited to just variants of the most promising compounds. *See, e.g.*, *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004) (obviousness does not require that the claimed invention be the "preferred, or the most desirable" choice.); *In re Lamberti*, 545 F.2d 747, 750 (C.C.P.A. 1976) ("all disclosures of the prior art, including unpreferred embodiments, must be considered.").

Every compound that is disclosed in the prior art belongs to the public. The public is also entitled to be able to make obvious modifications of those prior art compounds. Requiring the skilled artisan to be motivated in the first instance to select the most promising prior art compound is not grounded in Section 103 or Supreme Court precedent. *See KSR*, 127 S. Ct. at 1741. As such, the LCA should not be required in the proper analysis of the obviousness of compound claims like those in the '532 Patent.

The PTO has not followed a rigorous LCA approach. In fact, this Board's predecessor stated that the LCA "is not the exclusive test for compound obviousness," and the evidence is "appropriately examined under the ... *Dillon* principle …." *Ex parte Cao*, No. 2010-00408 at 8-9 (B.P.A.I. Sept. 21, 2011).

Rather, the term "lead compound" has been interpreted by the Board in a way that does not require a greater showing of beneficial properties, essentially applying cases like *Dillon*. *See, e.g.*, *Ex parte Jimenez Mayorga*, No. 2010-012157 (B.P.A.I. Sept. 30, 2011); *Ex parte Gaul*, No. 2011-008222, 6 (B.P.A.I. Jan. 5, 2012); *Ex parte Dong*, No. 2011-010047 at 1 (P.T.A.B. Jan. 28, 2013). This has allowed the focus of the obviousness inquiry to remain on the closest structurally similar prior art compounds having some beneficial utility. In short, under the proper analysis, the POSA starts with the closest chemical structure in the prior art. *See In re Grabiak*, 769 F.2d 729, 731 (Fed. Cir. 1985) (structural similarity and a motivation to make the claimed compositions can suffice to allege a prima facie case of obviousness); *Dillon*, 919 F.2d at 696 (holding that a presumed expectation arises because structurally similar compounds have similar properties); *see also Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1360-61 (Fed. Cir. 2007) (proceeding to find patent invalid as obvious by starting analysis with closest prior art); *In re Huston*, 308 F.3d 1267, 1278 (Fed. Cir. 2002) (same).

2. Because Mirabegron was Obvious, Each of the Challenged Claims are Unpatentable.

Claim 5 is directed to the mirabegron compound or salts thereof. As demonstrated below, claims 1, 3, 4, 6, 9 and 15 encompass mirabegron. Claims 11, 12, and 16 encompass a pharmaceutical composition comprising mirabegron and a pharmaceutically acceptable carrier. Thus, if mirabegron (and its use in

pharmaceutical compositions) is obvious under 35 U.S.C. § 103, then all of these claims are obvious. *See, e.g.*, *In re Muchmore*, 433 F.2d at 824-25.

By October 1997, the earliest priority date of the '532 patent, a POSA would have considered it obvious to make mirabegron, and would have had a reasonable expectation that it would have a beneficial pharmacological utility. Therefore, each claim challenged in this Ground 1 includes obvious subject matter.

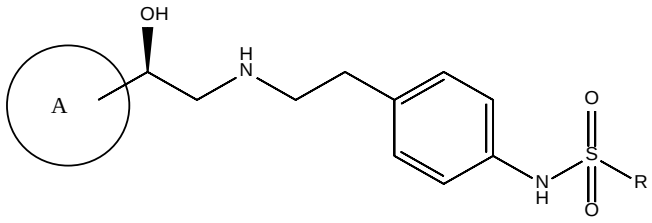
3. "Compound" Claims 1, 3-6, 9, and 15 were Obvious Because a POSA Would Have Been Motivated to Make Mirabegron with a Reasonable Expectation of Success.

Under *Dillon* and related Supreme Court precedent, the proper obviousness analysis considers the most structurally similar chemical compound in the prior art. Here, that compound is described in Merck US197.

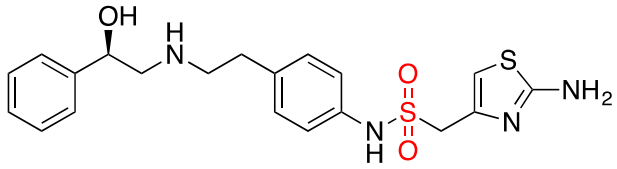
The POSA would be drawn to Merck US197 and its teachings for several reasons. *First*, a POSA would have understood that Merck is a large and well-respected research pharmaceutical company. Merck's research of selective β_3-AR agonists with positive results worthy of patent protection would signal the disclosed compounds should be considered for further development. *See* Ex. 1002 at ¶130. *Second*, a POSA would have also recognized that the type of assays used to determine β_3 selectivity was important. *See* Ex. 1008 at Col. 1:50-58 ("it has become apparent that the rodent is not a good model for predicting human β3 selectivity."); *see also* Ex. 1002 at ¶131. A POSA would look to the compounds of

Merck US197 because they are described as beneficial compounds based on more accurate methods of testing β3-selectivity employing cloned human β3 receptors, as opposed to outdated rodent models. *See* Ex. 1008 at Col. 1:59-67; Ex. 1002 at ¶131.

As described below, a preferred subgenus of Merck US197 was:



One of the prior art compounds encompassed by this preferred subgenus in Merck US197 that would be envisioned by the POSA is:

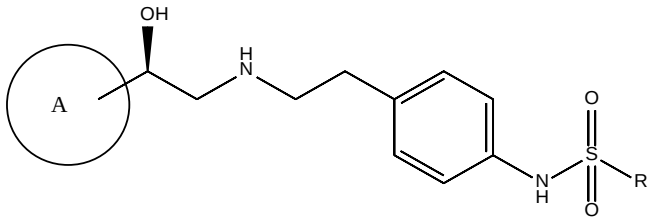


This compound differs from mirabegron solely in that it is a sulfonamide, not an amide (where the highlighted sulfonyl (SO_2) group is replaced with a carbonyl (C=O)). This compound will be referred to herein as "mirabegron sulfonamide." Also described below is why a POSA would have been motivated to change mirabegron sulfonamide to mirabegron and have a reasonable expectation that mirabegron would possess a useful pharmaceutical activity.

a. Merck US197 Disclosed Mirabegron Sulfonamide and its Utility as a β3-Agonist.

Merck US197 disclosed a core structural framework for a number of compounds that have utility as selective β3-agonists. *See, e.g.*, Ex. 1008 at abstract; Ex. 1002 at ¶134. Like the '532 patent, Merck US197 disclosed a large genus of compounds with a smaller number of examples and disclosed that all compounds that fall within the genus had selective β3-agonist activity. Ex. 1002 at ¶134; Ex. 1008 at abstract; Ex. 1001 at Col. 2:23-30.[7]

A POSA would consider the structure shown below as the preferred "core structure" of Merck US197 for the following reasons:



[7] In considering what the POSA would be taught from the Merck US197 disclosure, Astellas has implicitly admitted that the POSA's skill level, and especially her ability to recognize the specific compounds that are disclosed in a broader genus, is very high. For example, the disclosure of the '532 patent itself is quite similar to Merck US197 in that the '532 patent specification claims a genus of hundreds of thousands of compounds while specifically disclosing a subset of only 113 examples. Ex. 1001 at Cols. 16:5-28:67; Ex. 1002 at ¶134, n.11. For the genus claims of the '532 to be enabled and have sufficient written description, a POSA must be able, from the '532 patent's description of the genus, substitution options, and limited specific examples, to envision compounds disclosed as options of the core structure. The POSA must, therefore, be able to do the same for Merck US197.

See Ex. 1008 at Col. 4:25-34. *First*, a POSA would know the stereoisomer depicted is preferred. *Id.* at Col. 15:19-20 ("the following stereospecific structure represents the preferred stereoisomers of the instant invention."); *see also* Ex. 1005 at 2821; Ex. 1002 at ¶135.

Second, a POSA would consider this the core structure in Merck US197 because the vast majority of the disclosed specific examples utilize it. All of the examples in Tables 1, 2, 3, 4, 5, and 6 utilize that stereoisomer, hydrogen for R^4, R^5, and R^6, and an ethylene group between the amine and the phenyl ring. Ex. 1002 at ¶135; Ex. 1008 at Col. 33:4-35; 41:34-45:57; Col. 46:1-21; Col. 47:4-20; Col. 49:4-29; Col. 52:36-53:17. Also, all of the examples disclosed in the Tables, except for the two in Table 4, utilize hydrogen at R^2 and R^3. *Id.*

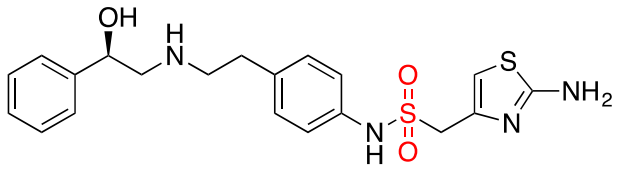
From this core sub-genus, a POSA would be able to envision and understand that the "A" group in the above structure includes phenyl because Merck US197 teaches and specifically identifies phenyl as being a "more preferred" substituent for A. Ex. 1008 at Col. 15:61-15:63 (identifying phenyl at the "A" position as being one of the "more preferred values."); Ex. 1002 at ¶136. The use of phenyl for A is also specifically identified in other portions of the Merck US197 patent. *See, e.g.*, Ex. 1008 at Table 3, Examples 90-92; Col. 46:1-46:21; Ex. 1002 at ¶136. The phenyl group is also included in the first three of the specifically claimed compounds of claim 12, which a POSA would look to in considering preferred

substitutions and envisioning the disclosures of Merck US197. Ex. 1008 at Col. 56:22-29; Ex. 1002 at ¶136. In addition, the phenyl "A" group would be consistent with the minimal pharmacophore disclosed in Blin (Ex. 1006), and thus would be envisioned by the POSA in understanding the teachings of Merck US197.

Astellas has made binding admissions that a POSA would be able to envision the "A" is phenyl. During prosecution, Astellas admitted that Example 8 of Merck WO161 (Ex. 1012) "differs from the compounds encompassed by claims 1-5, 7-11, 13, and 14 of the '532 Patent in that it has, on the left hand side of the molecule, a hydroxyl-substituted phenyl ring-O-CH_2-CH(OH)-CH_2(NH), rather than a phenyl ring-CH_2-CH(OH)-CH_2(NH) without the hydroxyl substitution … [and] on the right hand side of the molecule, a-N(H)-S(O_2)-phenyl ring, while the compounds encompassed by claims 1-5, 7-1, 13 and 14 of the '532 Patent have a –N(H)-C(O)-heteroaryl ring (optionally substituted)." *See* Ex. 1007. at PTO_00001117-18. Astellas also admitted that Blin arguably taught that "there is no need to include hydroxyl substituent on the phenyl ring of these pharmacophores." *Id.* at PTO_00001118.

A POSA would also have envisioned and understood that the "R" group disclosed in Merck US197 includes a 2-amino-thiazol-4-yl group. For example,

Merck US197 taught that "[t]he more preferred values of Z[8] are … thiazolyl …" (Ex. 1008 at Col. 15:64-16:5; Ex. 1002 at ¶137) and that short alkyl spacers can be used between the sulfonamide and the R group while still retaining selective β3-agonist activity, as demonstrated by the formula allowing for $-SO_2(CH_2)_r-R^7$, where r can be 0 to 3, and preferably is 0 to 2 (Ex. 1008 at Col. 2:15-27; Col. 4:25-34; Ex. 1002 at ¶137). A POSA would thus be able to read the description of potential substitutions on the core structure disclosed in Merck US197 and understand that mirabegron sulfonamide is disclosed and enabled:



Ex. 1002 at ¶138.

A POSA would have expected the disclosed mirabegron sulfonamide to be a selective ß3-adrenergic receptor agonist with useful pharmacological activity. For example, Merck US197 disclosed that all of the disclosed sulfonamides, including mirabegron sulfonamide, were selective ß3-agonists useful in the treatment of diabetes and obesity. *See* Ex. 1008 at Abstract; Ex. 1002 at ¶139. Again, Astellas made binding admissions in relation to the similar disclosure of Merck WO161 (Ex. 1012). Astellas admitted that the shared specification "describes a group of

[8] As described above, R is shorthand for "$(CH_2)_r-R^7$. R^7 is defined in the '532 patent as Z-(R_{1a})n and R_{1a} can be $-NH_2$. Ex. 1008 at Cols. 3:15-18; 2:41; 2:46; 3:52-53; 4:30.

substituted sulfonamides that are said to be selective β3-adrenergic receptor agonists having very little β1 and β2 adrenergic receptor activity that are expected to be useful in the treatment of Type II diabetes." Ex. 1007 at PTO_00001117.

In addition, a POSA would have reasonably expected mirabegron sulfonamide to be an active and selective β3-agonist because, as discussed in Section I.B above, a POSA would have known it had the Blin "minimal pharmacophore" necessary for selective β_3-AR activity and would have reasonably expected success in maintaining selectivity for the β_3-AR if the minimal pharmacophore was present in a compound and maintained throughout modifications of it. *See* Ex. 1002 at ¶140; Ex. 1006 at 1102; *see also* Ex. 1007 at PTO_00001116 (Astellas admitting Blin "discusses the structural-activity features responsible for the β_3 potency and selectivity of ligands."); *id.* at PTO_00001474 (Examiner stating Blin taught that "[p]otent β_3 adrenergic receptor agonists may have one of the following [two] minimal pharmacophores …."). A POSA would have reasonably expected mirabegron sulfonamide to be an active and selective β3-agonist because it met all the Blin requirements, namely (i) an aromatic group, (ii) a beta-hydroxyl function, and (iii) a protonated amine. *See, e.g.*, Ex. 1006 at 1101-02, Figure 7; Ex. 1002 at ¶140. Further, the POSA would have expected mirabegron sulfonamide to have β3-agonist selectivity because it had a long and bulky amine substituent, which Blin taught "determined" β_3 activity. *See, e.g.*, Ex.

1002 at ¶140; Ex. 1006 at 1099, 1103. Finally, the POSA would have known that "[t]he stereochemistry of the phenethanolamine has a crucial influence on the potency and selectivity …" and that the R optical isomer at the chiral carbon in the minimal pharmacophore possessed by mirabegron sulfonamide was strongly preferred. *See, e.g.*, Ex. 1002 at ¶141; Ex. 1005 at 2821.

b. A POSA Would Have Been Motivated to Change the Sulfonamide into an Amide with a Reasonable Expectation of Success in Making Mirabegron and It Being a Selective β3-Agonist.

Envisioning the mirabegron sulfonamide disclosed in Merck US197, a POSA would have been motivated to replace the sulfonamide with an amide using bioisosteric replacement (hereinafter, "the Amide Substitution") and have a reasonable expectation of success in both making mirabegron and it having pharmacological utility.

Motivation to Make the Amide Substitution

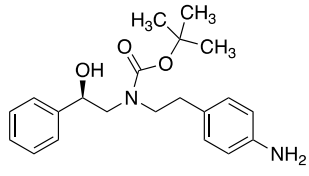
One of the most straightforward changes a POSA would have made is to replace the sulfonamide with an amide using bioisosteric replacement. Ex. 1002 at ¶143. As taught by both Thornber (Ex. 1017) and/or Silverman (Ex. 1016), bioisosterism was a well-known tool used in lead modification approach to drug discovery that "allow[s] molecular modifications, in which the number of variables changed are limited" (Ex. 1017 at 565-66) that "are useful in searching for potency, selectivity, absorption, and duration" (*id.* at 567) and "that has been

shown to be useful to attenuate toxicity or to modify the activity of a lead [compound]" (Ex. 1016 at 19). Ex. 1002 at ¶143. Further, a POSA would know that using bioisosteric replacement can result in modifications to the lead compound that produce "broadly similar biological properties." Ex. 1017 at 563-64; *see also* Ex. 1016 at 19; Ex. 1002 at ¶143. Thornber and Silverman taught that the carbonyl (-C=O) group is a bioisostere for a sulfonyl ($-SO_2$) group. *See* Ex. 1017 at 569, Table 3; Ex. 1016 at 20, Table 2.3; Ex. 1002 at ¶144. Because they were bioisosteres, a POSA would be motivated to make the Amide Substitution. Ex. 1002 at ¶144; *see also* Ex. 1007 at PTO_00001475 (Examiner finding same motivation in light of Thornber).

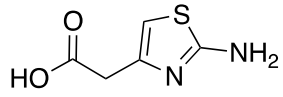
Further motivation to make the Amide Substitution stems from a POSA wanting to maintain other parts of the molecule. For instance, a POSA would want to maintain the Blin minimal pharmacophore because it was responsible for the selective β3-agonism. Ex. 1002 at ¶145. The POSA would have been further motivated to make the Amide Substitution because (a) the majority of selective β3-agonists disclosed in Merck US197 had the ethylphenyl backbone, suggesting to the POSA that it was important for activity and (b) the sulfonamide was as far from the active pharmacophore as possible, which a POSA would reasonably expect to have the least chance eliminating or significantly lowering its agonist activity. *Id.* at ¶145.

A POSA would also make this substitution because the synthetic chemistry to make amides is straightforward and routine. *See* Ex. 1002 at ¶146; Ex. 1018 at Cols. 27:50-35:15 (disclosing synthesis of pharmaceutically useful compounds having the Blin minimal pharmacophore and similar structures to the compounds of Merck US197 except with amides in place of the sulfonamides in Merck). More specifically, a POSA would have known the sulfonamide substituent can be replaced with an amide based on a slight modification to the synthesis disclosed in Merck US197. For example, following Examples 92, 17, 18, and 25 of Merck US197 would give (R)-N-[2-[4-(aminophenyl)]ethyl]-2-hydroxy-2-(phenyl)ethylcarbarnic acid 1,1-dimethylethyl ester.[9] *See* Ex. 1008 at Col. 45:59-46:21; Col. 34:49-35:34; Cols. 37:55-38:23; Ex. 1002 at ¶146. The POSA would react this prior art compound with the appropriate carboxylic acid[10] in a manner similar to that described in Example 25 of Merck US197 with a reasonable expectation of making mirabegron. *See* Ex. 1002 at ¶146; Ex. 1008 at Col. 37:55-38:24, Example 25. In fact, similar reactions were taught in introductory organic chemistry classes to sophomores in college by October 1997. *See, e.g.*, Ex. 1002 at

---

[9] 

; Ex. 1002 at ¶146.

[10] 

, which was commercially available in 1997. Ex. 1024 at 103; Ex. 1002 at ¶146.

¶146; Ex. 1019 at 999 (discussing synthesis of amides by reacting amines with acyl chlorides).

Astellas' admissions during reexamination are again informative. There, Astellas admitted that Thornber "teaches that a carbonyl group (-CO) may be replaced with a sulfoxide [sic][11] group (-SO2)." *See* Ex. 1007 at PTO_00001118. Further, Astellas admitted that "it arguably might have been considered prima facie obvious, based on the teachings of Blin, Thornber and JP '861 to modify the compound disclosed in Example 8 of Merck WO161 to arrive at the claimed invention." *Id*. at PTO_00001119. It similarly would have been obvious to modify the mirabegron sulfonamide in such a way.

Reasonable Expectation of Success

A POSA would also have had a reasonable expectation of success that making the Amide Substitution would result in mirabegron and that mirabegron would have beneficial pharmacological activity as a selective β3-agonist. *First*, mirabegron is structurally similar to the mirabegron sulfonamide (and the other structurally similar compounds disclosed) in Merck US197 that are taught as selective ß3-agonists. *See* Ex. 1008 at Abstract; Col. 4:25-39; Col. 15:13-31; Col. 6:33-7:1; Col. 15:61-16:5. This structural similarity would give a reasonable

[11] The proper chemical name for the SO_2 group is "sulfone" and therefore Applicants should have referred to it as either a sulfone or sulfonyl group. Ex. 1002 at ¶ 147, n.14. However, a POSA would have understood Applicants' point given their inclusion of the "(-SO_2)." *Id.*

expectation of similar activity. *Second*, both mirabegron and mirabegron sulfonamide included the Blin minimal pharmacophore required for selective ß3-receptor agonism. Ex. 1006 at 1102. The POSA would not expect that the substitution of the amide for the sulfonamide to drastically change the length or reduce the flexibility of the molecule, and thus stayed with Blin's teachings for this portion of the molecule. *Third*, bioisosteric replacement was known to give compounds with "broadly similar biological properties." Ex. 1017 at 563-64; *see also* Ex. 1016 at 19; Ex. 1002 at ¶151.

Fourth, the POSA's skill level was high and there were more structural differences within Merck US197 (*i.e.*, between mirabegron sulfonamide and other disclosed compounds) and within the '532 patent (*i.e.*, between mirabegron and other compounds in the genus of claim 1) than between mirabegron sulfonamide and mirabegron. Ex. 1002 at ¶152. If the POSA had a reasonable expectation that the full scope of Merck US197 and the '532 are enabled and described, then the POSA would also have had a reasonable expectation from Merck US197 that mirabegron would have a beneficial utility.

Fifth, if a POSA had any question as to whether mirabegron sulfonamide or its modified version (*i.e.*, mirabegron) had activity, he or she would simply perform tests well known in the art to determine efficacy such as those disclosed in Merck US197. *See* Ex. 1002 at ¶153; Ex. 1008 at Col. 1:59-67; *see also* Ex. 1010

at Col. 2:1-11; Col. 23:63-25:17. Applicants admitted as much during prosecution. *See* Ex. 1015 at PTO_00000665-66 (asserting POSA would be able to conduct tests if it had any questions regarding efficacy).

Finally, during reexamination, Astellas admitted that a POSA would have a reasonable expectation of success. Ex. 1007 at PTO_00001119 ("there arguably might have been … a reasonable expectation that these modifications could be made without adversely affecting the utility of the compound for treating diabetes.").

Because mirabegron is a compound within the scope of claims 1, 3-6, 9, and 15 of the '532 patent, and a POSA would have been motivated to make mirabegron with a reasonable expectation of succeeding and that it would be a useful and selective β3-agonist, those claims are invalid as obvious.

4. <u>"Composition" Claims 11, 12, and 16 Were Obvious Because a POSA Would Have Been Motivated to Make a Composition Comprising Mirabegron and a Pharmaceutical Carrier with a Reasonable Expectation of Success.</u>

The POSA would have been motivated and have had a reasonable expectation of success in making a composition comprising mirabegron and a pharmaceutically acceptable carrier, which would fall within the scope of the compositions claimed in Claims 11, 12, and 16, for at least three reasons.

First, the POSA would have had a reasonable expectation that mirabegron had beneficial pharmacological activity, especially as a selective β3-agonist, which

was useful for treating diseases (*e.g.*, diabetes, obesity, etc.). As discussed above, Merck US197 disclosed structurally similar compounds that were "selective β_3 adrenergic receptor agonists with very little β_1 and β_2 adrenergic receptor activity" that had "potent activity in the treatment of Type II diabetes and obesity." Ex. 1008 at Abstract; *see also id.* at Col. 28:16-17; Ex. 1002 at ¶158. Also, a POSA would know that mirabegron has the minimal pharmacophore and flexible backbone for selective β_3 AR agonism. *See* Ex. 1002 at ¶158; Ex. 1006 at 1099-1103. This expectation of beneficial pharmacological activity and disease treatment would have motivated the POSA to formulate mirabegron into a composition for treatment. *See* Ex. 1002 at ¶158.

Second, a POSA would have known of many routine ways to make compositions and used common pharmaceutical excipients, such as pharmaceutically acceptable carriers. *See id.* at ¶159.

Third, the prior art explicitly disclosed and taught how to make and use compositions comprising such carriers that contained structurally similar selective β_3 AR agonists useful for treating diseases (*e.g.*, diabetes, obesity, etc.). *See, e.g.*, Ex. 1002 at ¶160; Ex. 1008 at Col. 29:1-3; Col. 29:47-30:64; *see also* Ex. 1009 at Abstract; Col. 2:5:7; Col. 17:51-18:49; Col. 68, Claim 18; Ex. 1010 at Abstract; Col. 10:23-33; Col. 21:15-22:55; Col. 40, Claim 10; Ex. 1011 at Col. 15: 57-61; Claim 24.

Thus, a POSA would have been motivated to formulate mirabegron into compositions with a pharmaceutically acceptable carrier. *See* Ex. 1002 at ¶161.

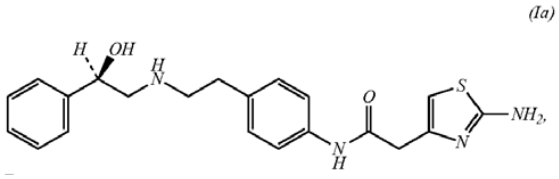
A POSA doing so would have a reasonable expectation of success in both making such a composition and it being a useful pharmaceutical treatment at least because (a) the prior art taught that similar compounds could be formulated in a variety of formulations with many different carriers and still be selective β_3 AR agonists useful for treating diseases (*e.g.*, diabetes, obesity) and (b) a composition comprising an API and a carrier is a very common and routine composition that a POSA could make with ordinary and routine methods known in the art. *See, e.g.*, Ex. 1002 at ¶161; Ex. 1008 at Col. 29:1-3; Col. 29:47-30:64; *see also* Ex. 1001 at Col. 12:12-15 (admitting "[a] pharmaceutical composition containing one or more of the compound [sic] of the present invention or the salt thereof as an effective ingredient is prepared using common pharmaceutically acceptable vehicles."). As such, Claims 11, 12, and 16 of the '532 patent were obvious.

5. Conclusion of Ground 1.

In view of the foregoing, each of Claims 1, 3-6, 9, 11, 12, 15, and 16 are obvious over Merck US197, in view of Blin, in combination with Thornber and/or Silverman, in view of a POSA's general knowledge and skill in October 1997. The rationale to combine these teachings, discussed above, with a reasonable

expectation of success, provide the basis for finding each of these claims unpatentable under 35 U.S.C. § 103.

The following claim chart shows where each component of the compound of Claim 5 and the composition of Claim 11 are disclosed in at least Merck US197 and Thornber and/or Silverman. As shown above, because Claims 5 and 11 are the narrowest claims and obvious, "the broader claims must likewise be obvious." *Muchmore*, 433 F.2d at 824-25.

Challenged Claims	Exemplary Invalidating Prior Art
Claim 5	
A compound of formula (Ia):  (Ia) or a salt thereof.	It would have been obvious to a POSA to make mirabegron. Mirabegron is the compound depicted in formula (Ia) of claim 5. For example, Merck US197 disclosed a preferred genus that encompassed mirabegron sulfonamide. Ex. 1008 at Col. 4:25-34; Col. 3:15-18; 2:41; 2:46; 3:52-53; 4:30; Col. 15:13-31, Col. 6:33-7:1; Col. 15:64-16:5; Ex. 1002 at ¶¶128-141. Merck US197 also disclosed that the disclosed sulfonamides, which included mirabegron sulfonamide, had a beneficial pharmacological activity, especially as a selective β3-agonist, that were useful for treating diseases. *See, e.g.*, Ex. 1008 at Abstract, Col. 2:15-4:14. Also, Blin identified a "minimal pharmacophore" necessary for selective β_3-AR activity that included

	(i) an aromatic group, which could stabilize aryl-aryl interactions, (ii) a beta-hydroxyl or an ether function, which could establish a hydrogen bond, and (iii) a protonated amine, which should create an ionic bridge with a negatively charged carboxyl function inside the pocket site. *See* Ex. 1006 at 1101-02. Thornber and/or Silverman taught a POSA that replacement of the sulfonamide with an amide was bioisosteric and, thus, would be a useful way to find a new compound with beneficial pharmacological activity, especially as a selective β3-agonist, useful for treating diseases. *See* Ex. 1017 at 563-66, 569; Ex. 1016 at 19-20.
Claim 11	
A composition comprising the compound of formula (Ia) or the salt thereof as claimed in claim 5, in a pharmaceutically acceptable carrier.	It would have been obvious for a POSA to make mirabegron, which is the compound of formula (Ia) of claim 5. *See* above for claim 5, which is incorporated by reference as if set forth fully herein. It would have been obvious for a POSA to make a composition of mirabegron that included a pharmaceutically acceptable carrier because the POSA would have had a reasonable expectation that mirabegron would have a beneficial pharmacological activity as a selective β3-agonist, which is useful for treating diseases (*e.g.* diabetes, obesity, etc.) and Merck US197 (and other prior art) taught oral administration of similar

	compounds for such treatments as compositions (*e.g.* tablets) comprising pharmaceutical acceptable carriers. *See*, *e.g.*, Ex. 1008 at Abstract, Col. 28:16-30, 29:47-30:44; Col. 56, Claim 11; *see also* Ex. 1009 at Abstract; Col. 2:5:7; Col. 17:51-18:49; Col. 68, Claim 18; Ex. 1010 at Abstract; Col. 10:23-33; Col. 21:15-22:55; Col. 40, Claim 10; Ex. 1011 at Col. 15: 57-61; Claim 24.

B. [Ground 2] Claims 1, 3-6, 9, 11, 12, 15, and 16 Were Obvious Under 35 U.S.C. § 103 Over Merck US197, in view of Blin, in Combination with Merck US048 and Silverman and/or Thornber.

Alternatively, Claims 1, 3-6, 9, 11, 12, 15, and 16 of the '532 patent are invalid as obvious even applying the inappropriately rigid LCA framework. Under the LCA, "[a] court determines whether a chemist of ordinary skill would have selected the asserted prior art compounds as lead compounds, or starting points, for further development efforts." *Otsuka Pharm. Co. Ltd. v. Sandoz Inc.*, 678 F.3d 1280, 1291 (Fed. Cir. 2012). The Federal Circuit has somewhat tempered the rigidness of the lead compound analysis somewhat by stating that "the lead compound analysis must, in keeping with *KSR*, not rigidly focus on the selection of a single, best lead compound." *Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010).

As described in more detail below, the challenged claims were obvious because a POSA would have selected the compounds disclosed in Table 3 of

Merck US197 as lead compounds and would have been motivated to modify these compounds to make mirabegron with a reasonable expectation that it would have beneficial pharmacological activity as a selective β3-agonist similar to that of the Merck US197 lead compounds.

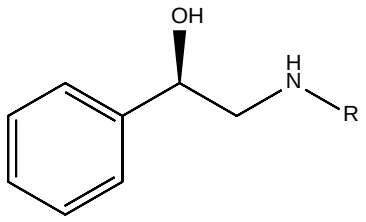
1. <u>"Compound" Claims 1, 3-6, 9, and 15 were Obvious Because a POSA Would Have Been Motivated to Make Mirabegron with a Reasonable Expectation of Success.</u>

a. A POSA Would Have Selected the Merck US197 Table 3 Compounds as Lead Compounds.

A POSA in October 1997 looking at β_3-AR agonists would have selected the three compounds in Table 3 of Merck US197 as lead compounds for at least the following reasons.

First, a POSA would have been motivated to use the "minimal pharmacophore" in Blin necessary for selective β_3-AR activity and would have reasonably expected success in maintaining β_3-AR selectivity if the minimal pharmacophore was present in the lead compound(s) and maintained throughout the modification of them. A POSA would have known from Blin that the structure-activity relationship of such agonists had been determined. *See, e.g.*, Ex. 1006 at 1102; Ex. 1002 at ¶168; *see also* Ex. 1007 at PTO_00001116 (Astellas stating Blin "discusses the structural-activity features responsible for the β_3 potency and selectivity of ligands."). Thus, a POSA would have chosen lead compound(s) that included (i) an aromatic group, which could stabilize aryl-aryl

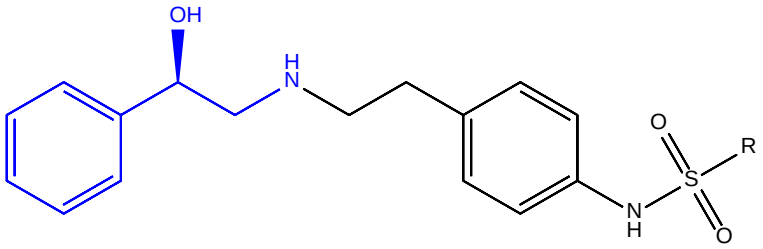
interactions, (ii) a beta-hydroxyl functionality, which could establish a hydrogen bond, and (iii) a protonated amine, which could create an ionic bridge with a negatively charged carboxyl function inside the pocket site. *See, e.g.*, Ex. 1006 at 1101-02, Figure 7; Ex. 1002 at ¶168; *see also* Ex. 1007 at PTO_00001116 (Astellas stating "Blin teaches that potent β_3-agonists may have the following minimal pharmacophore"); *id.* at PTO_00001474 (Examiner stating Blin taught that "[p]otent β_3 adrenergic receptor agonists may have one of the following [two] minimal pharmacophores …."). Further, the POSA would have been motivated by Blin's teaching to use a long and bulky amine substituent because Blin taught such substituents "determined" the β_3-AR activity. *See, e.g.*, Ex. 1006 at 1099, 1103; Ex. 1002 at ¶168. Also, the POSA would have known that "[t]he stereochemistry of the phenethanolamine has a crucial influence on the potency and selectivity …" and that the R optical isomer at the chiral carbon in the minimal pharmacophore was strongly preferred. *See, e.g.*, Ex. 1005 at 2821; Ex. 1008 at Col. 15:13-31, Compound Ic; Col. 55, Claim 3; Ex. 1002 at ¶168. Thus, a POSA looking for a new β3-AR agonist would have been looking for leads with the following structure:



where R is a long and bulky chain that is flexible enough to allow for extended conformations, which Blin taught "could be adopted in the less encumbered β_3 site [and] may induce agonistic effects." Ex. 1006 at 1103.

Second, armed with the above structure-activity relationship, a POSA would look at what large research-based pharmaceutical companies were doing in this area and see that Merck, a very large and well-respected research pharmaceutical company, was very active in selective β_3-AR agonists based on the phenylethanolamine minimal pharmacophore in Blin. Ex. 1002 at ¶169; *see, e.g.*, Ex. 1008; *see also* Exs. 1009, 1010, 1012-14. Upon closer review of the Merck patents and publications, the POSA would focus first on Merck US197 because the compounds disclosed and claimed therein had the minimal pharmacophore in Blin as well as long and bulky substituents on the amine. *See* Ex. 1002 at ¶170. The POSA would particularly focus on Compounds 90-92 because they are the first three of only eleven compounds specifically named and claimed in Claim 12 of Merck US197, and would reasonably expect a company like Merck to claim particularly useful compounds. Ex. 1002 at ¶171; Ex. 1008 at Col. 56:22-29.

Third, the POSA would also focus on Compounds 90-92 because they had the following structure:



This structure contains the Blin minimal pharmacophore (shown in blue) for selective β3-agonist activity and the R-configuration that Merck US197 (and other prior art references) taught was important for selective agonist activity as well. Ex. 1002 at ¶172; Ex. 1008 at Col. 15:13-31, Compound Ic; Col. 55, Claim 3; Ex. 1005 at 2821. Further, the POSA would note that the vast majority of the disclosed specific examples in Merck US197 have a core structure with hydrogens for R^2, R^3, R^4, R^5, and R^6 and an ethylene group between the amine and the phenyl ring. Ex. 1002 at ¶172; Ex. 1008 at Col. 33:4-35; 41:34-45:57; Col. 46:1-21; Col. 47:4-20; Col. 49:4-29; Col. 52:36-53:17. From this core sub-genus, a POSA would be able to envision and understand that the "A" group in the above structure should be phenyl because Merck US197 teaches and specifically identifies phenyl as being a "more preferred" substituent for A. Ex. 1008 at Col. 15:61-15:63 (identifying phenyl at the "A" position as being one of the "more preferred values."); Ex. 1002 at ¶172. The use of phenyl for A is also specifically identified in other portions of the Merck US197 patent. *See, e.g.*, Ex. 1008 at Table 3, Examples 90-92; Col. 46:1-46:21. The significance of the phenyl group is also highlighted by its inclusion in the first three of the specifically claimed compounds of Claim 12,

which a POSA would look to in considering preferred substitutions and envisioning the disclosures of Merck US197. Ex. 1002 at ¶172; Ex. 1008 at Col. 56:22-56:29. In addition, the phenyl "A" group would be consistent with the minimal pharmacophore disclosed in Blin, and thus would be envisioned by the POSA in understanding the teachings of Merck US197. Ex. 1002 at ¶172; Ex. 1006 at 1099-1103.

Fourth, the POSA would have further been motivated to use Compounds 90-92 as potential lead compounds because the amine portions (shown in black) are long and bulky chains that are flexible enough to allow for extended conformations, which Blin also taught induced agonistic effects. Ex. 1002 at ¶173; Ex. 1006 at 1099, 1103.

Finally, because Compounds 90-92 met all of the structural criteria for selective β3-agonist activity in Blin (which was also reinforced by Merck US197), the POSA would have had a reasonable expectation of success that Compounds 90-92 would be a selective β3-agonist, even without data showing its activity.[12] Ex. 1002 at ¶174.

[12] Notably, Applicants appear to agree that these compounds are appropriate lead compounds. For example, Applicants chose Compounds 90 and 92 from Merck WO159 (Ex. 1013) (which has the same specification as Merck US197 (Ex. 1008)) as comparators in the testing they allege shows unexpected results. *See* Ex. 1015 at PTO_00000666; Ex. 1001 at Col. 11:21-31. Also, Applicants never argued that these compounds were not appropriate lead compounds during prosecution or reexamination. *See generally* Exs. 1015 and 1007.

b. A POSA Would Have Been Motivated to Modify the Merck US197 Lead Compounds to Make Mirabegron With a Reasonable Expectation of Success.

The POSA would have been motivated to make a few modifications to the identified lead compounds of Merck US197.

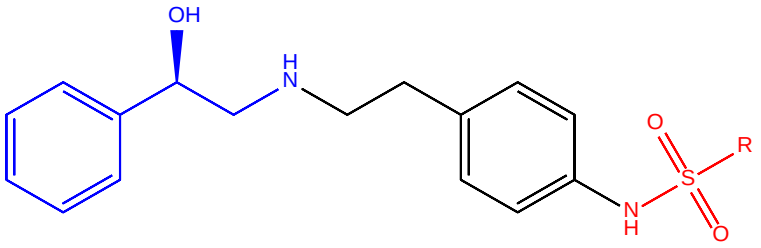
i. *Motivation to Make the Amide Substitution*

A POSA would make the Amide Substitution for all of the same reasons stated in Section V.A.3.b above, which is incorporated by reference herein, including the known bioisosterism of the carbonyl and sulfone groups and the desire to utilize bioisosteres in pharmaceutical development. Ex. 1002 at ¶¶142-155, 176.

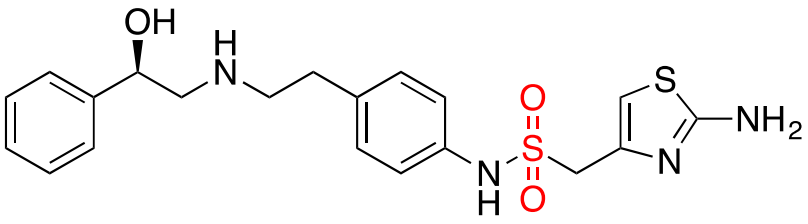
ii. *Motivation to Replace R with a 2-Amino-Thiazol-4-yl Group*

The POSA would have also been motivated to alter the substituent on the amide/sulfonamide portion of the compounds, shown in red below for numerous reasons. *First,* a POSA would have known to keep the Blin minimal pharmacophore (shown in blue below) intact and would have focused on the portion as far from the active pharmacophore as possible so as not to unnecessarily risk eliminating or significantly lowering its agonist activity. *See* Ex. 1002 at ¶177. *Second,* Examples 90-92 of Merck US197 suggested that beneficial alterations can be made on that portion of the molecule as that is the portion of the molecule being modified in these Examples. Ex. 1002 at ¶¶178. *Third,* a

substitution there is synthetically straightforward as the POSA could follow Examples 92, 17 and 18 of Merck US197 to get a protected R-phenethanolamine with the desired ethylphenyl backbone and a free amino group and react with the appropriate carboxylic acid (as discussed in Section V.A.3.b above, which is incorporated by reference herein). *Fourth*, the majority of selective β3-agonists disclosed in Merck US197 had the unsubstituted ethylphenyl backbone (shown in black below), suggesting to the POSA that it was important for activity. *See* Ex. 1002 at ¶179.



In choosing substituents to incorporate, a POSA would have been motivated to select a 2-aminothiazol-4-yl group as the R group in the structure above. For instance, in considering how to modify Examples 90-92, the POSA would consider other compounds that are part of a preferred subgenus of Merck US197. As described in Section V.A.3.a above, a POSA would have recognized the description of "mirabegron sulfonamide":



Recognizing this example and that it contains the key benefits of the disclosed compounds of Merck US197, the POSA would have modified Examples 90-92 to utilize the same 2-aminothiazol-4-yl group attached through a methyl.

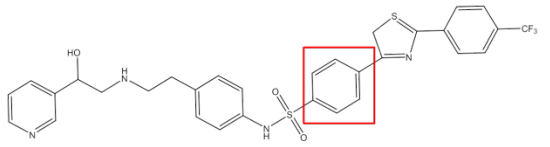
Furthermore, a POSA would have been motivated to select a thiazolyl group because Merck US197 identified thiazolyl as a "more preferred" group for that portion of the molecule. *See* Ex. 1008 at Col. 15:64-16:5 ("The more preferred values of Z are … thiazolyl …."); Ex. 1002 at ¶182. It also disclosed a number of thiazole-substituted compounds that were selective β_3-AR agonists compounds. *See, e.g.*, *id.* at Col. 9:15-17, Example 74; Col. 12:48-49; Col. 12:62-63; Col. 13:9-10; Ex. 1002 at ¶182.

Other prior art disclosures would have also led a POSA to use the 2–amino-thiazol-4-yl group. For example, Merck US048 (Ex. 1010) disclosed that "thiazole substituted benezenesulfonamides are β_3 adrenergic receptor agonists with very little β_1 and β_2 adrenergic receptor activity" that had "potent activity in the treatment of Type II diabetes and obesity." Ex. 1010 at Abstract; Col. 2:41-43; Col. 20:57-21:15; Ex. 1002 at ¶183. The POSA would have recognized that adding a thiazolyl group to the Merck US197 Table 3 structures would likely result in compounds that "are potent β_3-agonists, and have improved oral bioavailability in animals" over Merck US142 (Ex. 1014) (which has the same specification as Merck US197). Ex. 1010 at Col. 6:37-41; Ex. 1002 at ¶183. Specific selection of

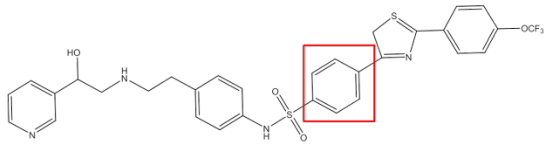
a 2–amino-thiazol-4-yl group is suggested by Merck US048, which taught that the preferred connectivity of the thiazole ring was at the C_2 (*i.e.* the carbon between the N and S) and C_4 (*i.e.* the carbon next to the N). *See* Ex. 1002 at ¶183; Ex. 1010 at Col. 5:12-14; *see also id.* at Col. 8:18-20, 39-41.

The POSA would have been taught to attach the 2-amino-thiazole to the sulfonamide/amide via a carbon-based spacer. For example, Merck US197 specifically taught that short alkyl spacers can be used between the sulfonamide and the R group while still retaining selective β3-agonist activity as demonstrated by the genus formula allowing for $-SO_2(CH_2)_r-R^7$, where r can be 0 to 3, and preferably is 0 to 2. *See* Ex. 1008 at Cols. 2:15-27; 4:23-34. Merck US048 also suggested the thiazole groups should be attached to the amide or sulfonamide through a carbon-based spacer. *See* Ex. 1002 at ¶185; Ex. 1010 at Cols. 2:55-4:46; 8:18-20, 39-41.[13] For example, Merck US048 disclosed several compounds had carbon-based spacers:

[13] A POSA would have combined the teachings of Merck US197 and US048 because (a) the compounds in both Merck US048 and US197 were structurally similar, (b) both sets of compounds were said to be selective β3-agonists; (c) both were said to be useful for treating the same types of diseases (*e.g.*, diabetes, obesity, etc.); and (d) both sets of compounds were synthesized in similar and compatible ways. Ex. 1002 at ¶184.



'048 Col. 8:18-20



'048 Col. 8:39-41

Ex. 1010 at Col. 8:18-20; 39-41 (spacer highlighted in red). While these specific examples of Merck US048 utilize a phenyl group as the carbon spacer, a POSA would have preferred using the more flexible methylene spacers of Merck US197 (Ex. 1008 at Col. 2:15-27; Col. 4:23-34) because Blin (Ex. 1006) taught that flexibility was beneficial to selective β3-agonist activity. *See* Ex. 1006 at 1099, 1103; Ex. 1002 at ¶186. A POSA would also have preferred to add a short alkylene spacer because that was a common method for medicinal chemists to develop new compounds from prior lead compounds. Ex. 1002 at ¶186; Ex. 1020 at 2244-45, 2246-47 (taking lead compound and varying length of alkyl spacer from two to six methylene groups resulting in increased affinity for receptor); Ex. 1021 at 93. Finally, such methylene spacers were disclosed in the core structure of Merck US197 discussed above and there is one in mirabegron sulfonamide.

A POSA would be further motivated to make such a substitution because 2-aminothiazol-4-yl was a known functional group that had been used in numerous other drugs. For example, Fujisawa (Astellas' predecessor) developed and sold

cefdinir in the early 1990s, which had the same 2-aminothiazol-4-yl group on it. Ex. 1022 at 299 ("Cefzon® (cefdinir, CFDN, Fujisawa Pharmaceutical Co., Ltd.) is an oral cephem antibiotic which was marketed in 1991."); Ex. 1002 at ¶187.[14]

iii. *Reasonable Expectation of Success*

A POSA would have had a reasonable expectation that making the alterations from Examples 90-92 to mirabegron would result in a compound with good pharmaceutical utility. A POSA would have had this expectation for the same reasons stated in Section V.A.3.b above, which are incorporated by reference herein. Also, such an expectation would be reasonable because mirabegron is structurally similar to and having all the known requirements of a selective β3-agonist as it (1) maintains the Blin pharmacophore, (2) is not drastically different in the length or flexibility of the substituent and thus stayed with Blin's teachings for this portion for the molecule; and (3) it would likely result in improved bioavailability of the compound, making it an effective treatment. *See* Ex. 1002 at ¶188.

Overall, based on the teachings of the prior art, the POSA would be motivated to make the Amide Substitution and substitute 2-aminothiazol-4-yl group as the R group, and would reasonably expect to make mirabegron and for it

[14] Other drugs containing a 2-aminothiazole group commercially marketed on or before October 1997 include carumonam, cefcapene, cefepime, cefetamet, cefotaxime, cefotiam, cefpodoxime, cefpirome, ceftazidime, ceftibuten, ceftriaxone, talipexole, pramipexole, and riluzole.

to have pharmacological activity as a selective β_3-agonist. Because mirabegron is a compound within the scope of claims 1, 3-6, 9, and 15 of the '532 patent, and a POSA would have had the motivation to make mirabegron with a reasonable expectation of success, those claims are invalid as obvious.

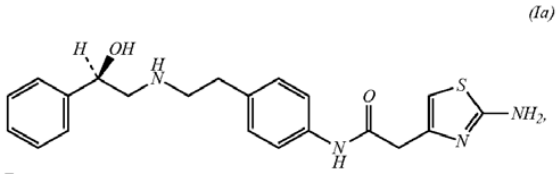
2. "Composition" Claims 11, 12, and 16 Were Obvious Because a POSA Would Have Been Motivated to Make a Composition Comprising Mirabegron and a Pharmaceutical Carrier with a Reasonable Expectation of Success.

The POSA would have had motivation and a reasonable expectation of success in making a composition comprising mirabegron and a pharmaceutically acceptable carrier, which would fall within the scope of the composition claimed in Claim 11, 12, and 16 for the reasons discussed in Section V.A.4 above (which is incorporated by reference as if fully set forth herein).

3. Conclusion of Ground 2.

In view of the foregoing, each of Claims 1, 3-6, 9, 11, 12, 15, and 16 were obvious based on the teachings of Merck US197, in view of Blin, and in combination with Merck US048, in further combination with Silverman (or Thornber), all in view of a POSA's general knowledge and skill in October 1997. The motivation to combine these teachings with a reasonable expectation of success, as discussed above, provides the basis for finding each of these claims unpatentable under 35 U.S.C. § 103.

The following claim chart shows where each component of the compound of Claims 5 and 11 are disclosed in at least Merck US197, Thornber or Silverman, and Merck US048. Because Claims 5 and 11 are the narrowest claims and obvious, "the broader claims must likewise be obvious." *Muchmore*, 433 F.2d at 824-25.

Challenged Claims	Exemplary Invalidating Prior Art
Claim 5	
A compound of formula (Ia):  (Ia) or a salt thereof.	It would have been obvious to a POSA to make mirabegron. Mirabegron is the compound depicted in formula (Ia) of claim 5. For example, a POSA would have selected the compounds of Merck US197 Table 3 as lead compounds at least because they had the Blin minimal pharmacophore, long, bulky amine substituents, and the preferred stereochemistry (*see, e.g.*, Ex. 1006 at 1101-02, 1099, 1103; Ex. 1008 at Col. 15:13-31, Claim 3; *see also* Ex. 1005 at 2821); they were the first three of only eleven compounds explicitly named and claimed in Claim 12 of Merck US197 (Ex. 1008); and/or Applicants tacitly admitted that these compounds were lead compounds (Ex. 1015 at PTO_00000666; Ex. 1001 at Col. 11:21-31). Merck US197 also disclosed that the disclosed sulfonamides, which included mirabegron sulfonamide, had a beneficial pharmacological activity, especially as a selective β3-agonist,

	that were useful for treating diseases. *See, e.g.*, Ex. 1008 at Abstract, Col. 2:15-4:14. A POSA would have modified the lead compounds in Merck US197 to have a 2-amino-thiazol-4-yl group as a substituent on the sulfonamide at least because Merck US197 identified thiazolyl as a "more preferred" group for that portion of the molecule (Ex. 1008 at Col. 15:64-16:5) and disclosed structurally similar thiazole-substituted compounds (*id.* at Col. 9:15-17, Example 74; Col. 12:48-49; Col. 12:62-63; Col. 13:9-10); Merck US197 disclosed a preferred subgenus that encompassed mirabegron sulfonamide (*id.* at Col. 4:25-39; Col. 15:13-31; Col. 6:33-7:1; Col. 15:61-16:5); Merck US048 disclosed structurally similar substituted thiazol-4-yl benzenesulfonamides that were potent and selective β3-agonists and had improved bioavailability (*see, e.g.*, Ex. 1010 at Abstract, Col. 2:41-43, Col. 20:57-21:15; 6:37-41; Col. 5:12-14; Col. 8:18-20, 39-41; Col. 2:55-4:46; Merck US197 and US048 taught that carbon-based spacers should be included between the sulfonamide and the aminothiazolyl group (*see, e.g.*, Ex. 1010 at Col. 8:18-20, 39-41; Ex. 1008 at Col. 1:15-27; Col. 4:23-34; see also Ex. 1006 at 1099, 1103; Ex. 1020 at 2244-47; Ex. 1021 at 93); and the synthesis of such compounds was straightforward following the teachings of Merck US197 (Ex. 1002 at ¶146; Ex. 1008 at Examples 92, 17, 18).

	Optionally, a POSA would have been further motivated to make this modification because other drugs, including Fujisawa's cefdinir, contained 2-aminothiazol-4-yl groups (Ex. 1022). Combining the teachings of Merck US197 and Merck US048, a POSA would have been motivated to make mirabegron sulfonamide with a reasonable expectation of success for the reasons stated above. With mirabegron sulfonamide in hand, Thornber and/or Silverman taught a POSA that replacement of the sulfonamide with an amide was bioisosteric and, thus, would be a useful way to find a new compound with beneficial pharmacological activity, especially selective β3-agonism, useful for treating diseases. *See* Ex. 1017 at 563-66, 569; Ex. 1016 at 19-20. A POSA would have been further motivated to make such a change and have a reasonable expectation of success for the reasons stated above.
Claim 11	
A composition comprising the compound of formula (Ia) or the salt thereof as claimed in claim 5, in a pharmaceutically acceptable carrier.	It would have been obvious for a POSA to make mirabegron, which is the compound of formula (Ia) of claim 5. *See* above for claim 5, which is incorporated by reference as if set forth fully herein. It would have been obvious for a POSA to make a composition of mirabegron that included a pharmaceutically acceptable carrier because the POSA would have had a

	reasonable expectation that these compounds would be selective β_3 AR agonists, which are useful for treating diseases (*e.g.* diabetes, obesity, etc.) and the prior art taught oral administration of similar compounds for such treatments as compositions (*e.g.* tablets) comprising pharmaceutical acceptable carriers. *See, e.g.*, Ex. 1008 at Abstract, Col. 28:16-30, 29:47-30:44; Col. 56, Claim 11; *see also* Ex. 1009 at Abstract; Col. 2:5:7; Col. 17:51-18:49; Col. 68, Claim 18; Ex. 1010 at Abstract; Col. 10:23-33; Col. 21:15-22:55; Col. 40, Claim 10; Ex. 1011 at Col. 15: 57-61; Claim 24

C. Secondary Considerations

With respect to each of the above grounds, Sawai is unaware of any evidence of objective indicia of nonobviousness with sufficient nexus to the challenged claims to rebut the strong *prima facie* obviousness of the challenged claims of the ’532 patent. For example, Sawai is not aware of any evidence to support an argument that (a) the claimed compounds or compositions satisfied a long felt, but unmet need, (b) others attempted the claimed subject matter and failed, (c) there was any skepticism of POSAs with respect to the subject matter of the challenged claims of the ’532 patent, (d) there was any licensing of the ’532 patent, (e) any commercial success of Myrbetriq® is reflective of non-obviousness of the challenged claims of the ’532 patent, (f) others have acquiesced to the validity of the ’532 patent, and/or (g) the industry has recognized the ’532 patent.

Defendants are also not aware of any evidence of unexpected results that demonstrate non-obviousness of the challenged claims. During prosecution of the original application, Applicants argued that the claimed compounds were unexpectedly superior to two prior art compounds in Merck WO159 in one specific assay. *See* Ex. 1015 at PTO_00000666; *see also* Ex. 1001 at Col. 11:21-31. Specifically, Applicants argued that "the compounds of the present invention were shown to have potentiating action to insulin selectivity ten times greater than those compounds [90 and 92] in WO 95/29159." *Id.* (citing specification). However, Astellas later admitted, during reexamination, that this statement was not true for all but two of the compounds encompassed by genera in Claims 1, 3, and 9. *See* Ex. 1007 at PTO_00001111-14. Neither of these compounds is mirabegron (*i.e.*, the only compound claimed in Claim 5 and one of the enantiomers claimed in Claim 4) and only one of the two is among the nine compounds claimed in Claim 6. Thus, this result (even if considered unexpected) is not commensurate with the scope of any of the challenged claims. *See*, *e.g.*, *In re Grasselli*, 713 F.2d 731, 741 (Fed. Cir. 1983).

Further, the greater activity in the insulin selectivity assay of the claimed compounds as compared to the two compounds from Merck WO159 belatedly disclosed by Astellas in the Supplemental Examination (Ex. 1007 at PTO_00001113) is merely a difference in degree, not a difference in kind and,

therefore, does not overcome the obviousness of the claimed compounds or compositions. *See, e.g., Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014) ("And 'differences in degree' of a known and expected property are not as persuasive in rebutting obviousness as differences in 'kind'— *i.e.*, a new property dissimilar to the known property."); *In re Merck*, 800 F.2d 1091, 1099 (Fed. Cir. 1986) (finding evidence that the new drug was a *more* potent sedative and *stronger* anticholinergic effect than the prior art was *insufficient* to outweigh the evidence of obviousness).

Also, the *en banc* Federal Circuit has explained "that an unexpected result or property does not by itself support a finding of nonobviousness." *Id.* at 976 (citing *In re Dillon*, 919 F.2d 688, 693, 697 (Fed. Cir. 1990) (en banc)).

Thus, these supposed unexpected results do not render claims 1, 3-6, 9, 11-12, 15 and 16 non-obvious at least because they are (a) not commensurate with the scope of the claims, (b) a difference in degree, not kind, and/or (c) standing alone, cannot overcome the strong *prima facie* case of obviousness above.

VI. GROUNDS FOR STANDING

Pursuant to 37 C.F.R. § 42.104(a), Sawai certifies that the '532 patent is available for *inter partes* review and that Sawai is not barred or estopped from requesting *inter partes* review of the '532 patent on the grounds identified. Sawai certifies that this Petition is served within one year of the date Sawai was served

with a complaint alleging infringement. Ex. 1023 (showing service on or after October 17, 2016).

VII. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8

Real parties-in-interest (§42.8(b)(1)): Sawai USA Inc. and Sawai Pharmaceutical Co., Ltd. are the real parties-in-interest for this petition. Sawai also notes that Sawai USA, Inc. is a wholly-owned subsidiary of Sawai Pharmaceutical Co., Ltd.

Related Matters (§42.8(b)(2)): Petitioners are both defendants in the following litigation involving, *inter alia*, the '532 patent: *Astellas Pharma Inc., et al. v. Sawai USA, Inc., et al.*, No. 16-cv-954-SLR (D. Del. 2016) as consolidated with *Astellas Pharma Inc., et al. v. Actavis Elizabeth LLC, et al.*, No. 16-cv-905-SLR (D. Del. 2016). Petitioners are aware that the '532 patent is also involved in the consolidated case between Astellas and Actavis (*Astellas Pharma Inc., et al. v. Actavis Elizabeth LLC, et al.*, No. 16-cv-905-SLR (D. Del. 2016)).

Lead and Back-Up Counsel (§42.8(b)(3)):

Lead Counsel: Brian J. Sodikoff (Reg. No. 54,697)

Back-Up Counsel: Martin S. Masar III (Reg. No. 62,007)

Service Information (§42.8(b)(4)): Petitioners consent to electronic service at the email addresses of lead and back-up counsel provided below:

Lead Counsel	Backup Counsel

Brian J. Sodikoff brian.sodikoff@kattenlaw.com KATTEN MUCHIN ROSENMAN LLP	Martin S. Masar III martin.masar@kattenlaw.com KATTEN MUCHIN ROSENMAN LLP
525 W. Monroe St. Chicago, IL 60661 Tel.: 312-902-5464 Fax: 312-902-1061	525 W. Monroe St. Chicago, IL 60661 Tel.: 312-902-5616 Fax: 312-902-1061

VIII. PAYMENT OF FEES UNDER 37 C.F.R. §§ 42.15(A) AND 42.103

The required fees are submitted herewith. If any additional fees are due at any time during this proceeding, the Office is authorized to charge such fees to Deposit Account No. 50-1214.

IX. CONCLUSION

For the reasons set forth above, Claims 1, 3-6, 9, 11-12, 15, and 16 of the '532 patent are unpatentable. Petitioner requests that *inter partes* review of these claims be instituted and that the claims be canceled.

Respectfully submitted,

Dated: October 16, 2017

/s/Brian J. Sodikoff

Brian J. Sodikoff, Lead Counsel
Reg. No. 54,697
Martin S. Masar III, Backup Counsel
Reg. No. 62,007
KATTEN MUCHIN ROSENMAN LLP

X. APPENDIX – LIST OF EXHIBITS

Exhibit No.	Description
1001	U.S. Patent 6,346,532 to Maruyama, *et al.* (issued February 12, 2002) with Reexamination Certificate for U.S. Patent No. 6,346,532 to Maruyama, *et al.* (issued February 24, 2015)
1002	Declaration of Robert M. Williams, Ph.D.
1003	*Curriculum Vitae* of Robert M. Williams, Ph.D.
1004	R. Howe, "β3-Adreneric agonists," Drugs of the Future, Vol. 18 (6), 529-549 (1993) ("Howe")
1005	K. Hattori, et al., "Asymmetric Synthesis of FR165914: A Novel β_3-Adrenergic Agonist with a Benzocycloheptene Structure," Bioorg. & Med. Chem. Lett., Vol. 5 (23), 2821-24 (1995) ("Hattori")
1006	Blin *et al.*, "Structural and Conformational Features Determining Selective Signal Transduction in the β3-Adrenergic Receptor," Molecular Pharmacol., 44, 1094-1104 (1993) ("Blin")
1007	File History of Supplemental Examination and Re-Examination of U.S. Patent No. 6,346,532 to Maruyama et al.
1008	'Fisher *et al.*, U.S. Patent No. 5,541,197, "Substituted Sulfonamides as Selective β_3-agonists for the Treatment of Diabetes and Obesity" ("Merck US197")
1009	Fisher, *et al.*, U.S. Patent No. 5,451,677, "Substituted Phenyl Sulfonamides as Selective β_3-agonists for the Treatment of Diabetes and Obesity ("Merck US677")
1010	Mathvink, *et al.*, U.S. Patent No. 6,011,048, "Thiazole Benzenesulfonamides as β_3-agonists for Treatment of Diabetes and Obesity ("Merck US048")
1011	Sher, U.S. Patent No. 5,321,036, "Thiazole and Oxazole-based β_3 Adrenergic Receptor Agonists" ("Sher")
1012	Fisher *et al.*, WO/1994/018161, "Substituted Phenyl Sulfonamides as Selective β_3-agonists for the Treatment of Diabetes and Obesity ("Merck WO161")
1013	Fisher *et al.*, WO/1995/029159, "Substituted Sulfonamides as Selective β_3-agonists for the Treatment of Diabetes and Obesity"

Exhibit No.	Description
	("Merck WO159")
1014	Fisher *et al.*, U.S. Patent No. 5,561,142, "Substituted Sulfonamides as Selective β_3-agonists for the Treatment of Diabetes and Obesity" ("Merck US142")
1015	File History of U.S. Patent No. 6,346,532 to Maruyama et al.
1016	Silverman, The Organic Chemistry of Drug Design and Drug Action, Academic Press, Inc. 1992, 19-23 ("Silverman")
1017	Thornber, "Isosterism and Molecular Modification in Drug Design" (1979) ("Thornber")
1018	Schromm *et al.*, U.S. Patent No. 5,223,614, "New Quaternary Ammonium Compounds, Their Preparation and Use" ("Schromm US614"**)**
1019	L.G. WADE, JR., ORGANIC CHEMISTRY 960-61, 999 (L. G. Wade, Jr. ed., 3d ed. 1995) ("Wade")
1020	R. C. Vollinga, et al., "New Analogs of Burimamide as Potent and Selective Histamine H_3 Receptor Antagonists: The Effect of Chain Length Variation of the Alkyl Spacer and Modificaitons of the N-Thiourea Substituent," J. Med. Chem., Vol. 38, 2244-50 (1995) ("Vollinga")
1021	GRAHAM L. PATRICK, AN INTRODUCTION TO MEDICINAL CHEMISTRY 82-110 (1st ed., Oxford University Press 1995) ("Patrick")
1022	K. Okamoto, "Clinical Efficacy of Cefzon® on Acute Otits Media in Children," Ear Nose Clinical, Vol. 92, 299-307 (1999) ("Okamoto")
1023	Complaint from *Astellas Pharma Inc., et al. v. Sawai USA, In*c., et al., No. 16-cv-954-SLR (D. Del. 2016)
1024	Aldrich Catalog Handbook of Fine Chemicals, (1988-1989) ("Aldrich")
1025	B. Hu & L. L. Jennings, "Orally Bioavailable β_3-Adrenergic Receptor Agonists as Potential Therapeutic Agents for Obesity and Type-II Diabetes," Prog. In Med. Chem., Vol. 41, 167-94 (2003) ("Hu & Jennings")

CERTIFICATE OF SERVICE

Pursuant to §§42.6(e) and 42.105(a), I certify that, on the 13th day of October, 2017, I caused to be served a true and correct copy of the foregoing Petition for *Inter Partes* Review (and accompanying Exhibits 1001-1025) by overnight courier, on Astellas Pharma Inc. at its correspondence address of record with USPTO as follows:

Astellas Pharma Inc.
3-11 Nihonbashi-Honcho 2-Chome,
Chuo-Ku, Tokyo, Japan

Copies of the above were also sent to Astellas Pharma Inc.'s litigation counsel via e-mail and FedEx. Copies were also served via FedEx on the other named Plaintiffs in the previously identified litigation.

Respectfully submitted,

Dated: October 16, 2017

/s/Martin S. Masar III
Martin S. Masar III, Backup Counsel
Reg. No. 62,007

CERTIFICATE OF WORD COUNT

Pursuant to 37 C.F.R. § 42.24(d), I certify that the above IPR Petition complies with the applicable type-volume limitation of 37 C.F.R. § 42.24(a)(1)(i). According to the word count feature of the word-processing system used to prepare this Petition, the Petition contains 12,177 words, excluding the parts of the brief exempted by 37 C.F.R. § 42.24(a)(1).

Respectfully submitted,

Dated: October 16, 2017

/s/Martin S. Masar III
Martin S. Masar III, Backup Counsel
Reg. No. 62,007