APPENDIX

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APPENDIX A

NOTE: This disposition is nonprecedential.

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

2017-2121

[Filed November 14, 2017]

UNITED THERAPEUTICS CORPORATION,
Appellant

v.

STEADYMED LTD.,
Appellee

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in No. IPR2016-00006.

JUDGMENT

STEPHEN MAEBIUS, Foley & Lardner LLP, Washington, DC, argued for appellant. Also represented by GEORGE ELLSWORTH QUILLIN; DOUGLAS H. CARSTEN, Wilson, Sonsini, Goodrich & Rosati, PC, San Diego, CA; ROBERT DELAFIELD, Austin, TX; SHAUN R. SNADER, United Therapeutics Corporation, Washington, DC.

STUART ERIC POLLACK, DLA Piper US LLP, New York, NY, argued for appellee. Also represented by LISA ANNE HAILE, STANLEY JOSEPH PANIKOWSKI, III, San Diego, CA.

THIS CAUSE having been heard and considered, it is

ORDERED and ADJUDGED:

PER CURIAM (PROST, *Chief Judge,* WALLACH and HUGHES, *Circuit Judges*).

AFFIRMED. *See* Fed. Cir. R. 36.

ENTERED BY ORDER OF THE COURT

November 14, 2017
Date

/s/ Peter R. Marksteiner
Peter R. Marksteiner
Clerk of Court

APPENDIX B

Trials@uspto.gov
571-272-7822

Paper No. 82
Entered: March 31, 2017

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Case IPR2016-00006

[Filed March 31, 2017]

STEADYMED LTD.,
Petitioner,

v.

UNITED THERAPEUTICS CORPORATION,
Patent Owner.

Case IPR2016-00006
Patent 8,497,393 B2

Before LORA M. GREEN, JONI Y. CHANG, and JACQUELINE T. HARLOW, *Administrative Patent Judges.*

HARLOW, *Administrative Patent Judge.*

App. 4

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

I. INTRODUCTION

Petitioner, SteadyMed LTD ("SteadyMed"), filed a Petition on October 2, 2015, requesting an *inter partes* review of claims 1–22 of U.S. Patent No. 8,497,393 B2 (Ex. 1001, "the '393 patent"). Paper 1 ("Pet."). Patent Owner, United Therapeutics Corporation ("UTC"), filed a Preliminary Response on January 14, 2016. Paper 10 ("Prelim. Resp.").[1] We determined that the information presented in the Petition demonstrated that there was a reasonable likelihood that SteadyMed would prevail with respect to at least one challenged claim. Pursuant to 35 U.S.C. § 314, we instituted trial on April 8, 2016, as to claims 1–22 of the '393 patent. Paper 12 ("Dec.").[2]

After institution, UTC filed a Patent Owner Response. Paper 31 ("PO Resp.").[3] SteadyMed filed a Reply to the Patent Owner Response. Paper 51 ("Pet. Reply").[4]

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[1] Paper 8 is a redacted version of the Patent Owner Preliminary Response.

[2] Paper 78 is a redacted version of the Decision on Institution.

[3] Paper 76 is a redacted version of the Patent Owner Response to Petition.

[4] Paper 52 is a redacted version of the Reply to Patent Owner's Response.

In addition, SteadyMed filed a Motion to Exclude Evidence (Paper 63, "Pet. Mot. Exclude").[5] UTC filed an Opposition (Paper 66, "PO Opp. Exclude"), and SteadyMed filed a Reply (Paper 72, "Pet. Reply Exclude"). UTC likewise filed a Motion to Exclude Evidence (Paper 65, "PO Mot. Exclude"). SteadyMed filed an Opposition (Paper 68, "Pet. Opp. Exclude"),[6] and UTC filed a Reply (Paper 71, "PO Reply Exclude").

Oral hearing was held November 29, 2016.

This final written decision is entered pursuant to 35 U.S.C. § 318(a). We have jurisdiction under 35 U.S.C. § 6.

We hold that SteadyMed has demonstrated by a preponderance of the evidence that claims 1–22 are unpatentable under 35 U.S.C. § 102(b) and 35 U.S.C. § 103(a). SteadyMed's Motion to Exclude is *dismissed*. UTC's Motion to Exclude is *denied*.

A. Related Matters

The '393 patent is asserted in several cases in the District of New Jersey. Pet. 1; Paper 4; Paper 15; Paper 21.

B. The '393 Patent

The '393 patent, titled "Process to Prepare Treprostinil, the Active Ingredient in Remodulin®,"

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[5] Paper 62 is a redacted version of Petitioner's Motion to Exclude Evidence.

[6] Paper 67 is a redacted version of Petitioner's Opposition to Patent Owner's Motion to Exclude Evidence.

issued July 30, 2013, from U.S. Patent Application No. 13/548,446 ("the '446 application") (Ex. 1002), filed July 13, 2012. Ex. 1001, [54], [45], [21], [22]. The '446 application is a continuation of U.S. Patent Application No. 12/334,731 ("the '731 application") (Ex. 1002), filed on December 15, 2008, now issued as U.S. Patent No. 8,242,305 ("the '305 patent"). Ex. 1001, [63]. The '393 patent claims priority to U.S. Provisional Patent Application No. 61/014,232 (Ex. 2008), filed December 17, 2007. Ex. 1001, [60].

The '393 patent recites 22 product-by-process claims for prostacyclin derivatives, including treprostinil.[7] *Id*. at 17:51–21:16; Pet. 5; Prelim. Resp. 3. The process disclosed by the '393 patent takes advantage of carbon treatment and salt formation steps to remove impurities, eliminating the need for purification by column chromatography. *Id*. at 17:29–32; *see also id*. at 5:41–45 ("[P]urification by column chromatography is eliminated . . . . [T]he salt formation is a much easier operation than column chromatography.").

The process for forming prostacyclin derivatives described in the '393 patent includes four steps: (a) alkylating a prostacyclin derivative to form an alkylated prostacyclin derivative; (b) hydrolyzing the alkylated prostacyclin derivative with a base to form a prostacyclin acid; (c) contacting the prostacyclin acid with a base to form a prostacyclin carboxylate salt; and

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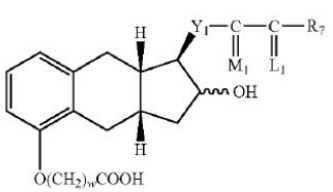
[7] The '305 patent, which issued from the parent to the application for the '393 patent, recites claims to a process for the preparation of prostacyclin derivatives comprising steps similar to those set forth in the product-by-process claims of the '393 patent. *Compare* Ex. 1001, 17:51–21:16, *with* Ex. 2007, 17:39–24:3.

(d) optionally reacting the prostacyclin carboxylate salt formed in (c) with an acid to form the desired compound, or pharmaceutically acceptable salt thereof. *Id*. at 1:65–3:19.

C. Illustrative Claim

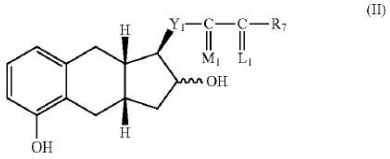
Each of the challenged claims is a product-by-process claim. Of the challenged claims, claims 1 and 9 are independent. Claim 1, reproduced below, is illustrative of the claimed subject matter.

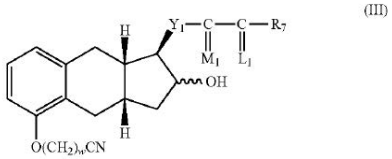
1. A product comprising a compound of formula I



or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising

a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III,

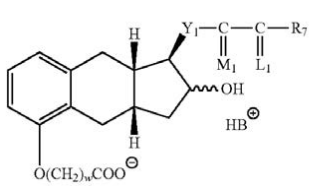




wherein [recitation of Markush groups for the specified structures],

b) hydrolyzing the product of formula III of step (a) with a base,

c) contacting the product of step (h)[8] with a base B to form a salt of formula I_s.



(Is)

and

d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula I.

Ex. 1001, 17:51–19:29. Claim 9 is drawn to a product comprising a specific treprostinil compound within the genus set forth in claim 1, and made by the process recited in claim 1. *Id*. at 19:48–20:46.

D. Prior Art Relied Upon

In its Petition, SteadyMed relies upon the following prior art references (Pet. 4–6):

Phares	WO 2005/007081 A2	Jan. 27, 2005 (Ex. 1005)

[8] We note that the reference to "step (h)," rather than "step (b)," in claim 1 is an apparent typographical error. *See* Ex. 1001, 3:66–67 ("(c) contacting the product of step (b) with a base B to for a salt of formula IV_s"); *see also* Pet. 25; Ex. 1009 ¶ 51.

Kawakami JP 56-122328A Sept. 25, 1981 (Ex. 1006)[9]

Moriarty et al., *The Intramolecular Asymmetric Pauson-Khand Cyclization as a Novel and General Stereoselective Route to Benzindene Prostacyclins: Synthesis of UT-15 (Treprostinil)*, 69 J. Org. Chem. 1890–1902 (2004) ("Moriarty") (Ex. 1004); and

Seyhan N. Eğe, ORGANIC CHEMISTRY 543–547 (2d ed. 1989) ("Eğe") (Ex. 1008).

E. Instituted Grounds of Unpatentability

We instituted the instant trial based on the following grounds of unpatentability:

Claims	Basis	Reference(s)
1–5, 7–9, 11–14, and 16–20	§ 102(b)	Phares
1–5, 7–9, 11–14, and 16–20	§ 103(a)	Moriarty and Phares
6, 10, 15, 21, and 22	§ 103(a)	Moriarty, Phares, Kawakami, and Eğe

[9] SteadyMed submitted a certified English translation of Kawakami as Ex. 1007. Exhibits 1011, 1019, and 1020 are translator declarations attesting to the accuracy of that translation.

II. ANALYSIS

A. Claim Construction

In an *inter partes* review, claim terms in an unexpired patent are given their broadest reasonable interpretation in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b). Under the broadest reasonable interpretation standard, claim terms are generally given their ordinary and customary meaning as would be understood by one of ordinary skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Under this standard, we may take into account definitions or other explanations provided in the written description of the specification. *In re Morris*, 127 F.3d 1048, 1054 (Fed. Cir. 1997). Any special definition for a claim term must be set forth in the specification with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Only those terms that are in controversy need be construed, and only to the extent necessary to resolve the controversy. *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999).

1. "A product comprising a compound [of/having] formula [I/IV] . . . or a pharmaceutically acceptable salt thereof" / "product"

Independent claims 1 and 9 recite the phrase "[a] product comprising a compound [of/having] formula [I/IV] . . . or a pharmaceutically acceptable salt thereof . . . ." In addition, each challenged dependent claim recites the term "product." In the Decision on Institution, we construed "[a] product comprising a

compound [of/having] formula [I/IV] . . . or a pharmaceutically acceptable salt thereof" to mean "a product including, but not limited to, a compound [of/having] formula [I/IV] or a pharmaceutically acceptable salt thereof." We additionally determined that the claim term "product," as it is used in the '393 patent, does not require interpretation because the claimed "product" is defined by the limitations recited in the challenged claims.

In its Patent Owner Response, UTC contends that our constructions of the above terms, as set forth in the Decision on Institution, are unreasonably broad. PO Resp. 13. In particular, UTC argues that we erred in interpreting the subsidiary term "comprising," as recited in the larger phrase "[a] product comprising a compound [of/having] formula [I/IV] . . . or a pharmaceutically acceptable salt thereof" to mean "including, but not limited to." *Id*. at 13–16. UTC also asserts that we erred in declining to construe "product" as "a substance resulting from a chemical reaction," and having the impurity profile conferred by the recited process steps. *Id*. at 16–18.

a. "Comprising"

UTC contends that the intrinsic evidence overrides the presumption that the transition phrase "comprising," as recited in the challenged claims, is an "open" phrase. *Id*. at 13. Although UTC does not identify which portions of the prosecution history or specification of the '393 patent support deviating from the well-established meaning of "comprising" in patent law, UTC nevertheless urges that review of the intrinsic record demonstrates disclaimer or disavowal

of an open-ended interpretation of "comprising." *Id*. at 13–16.

SteadyMed agrees with the construction of "comprising" set forth in the Decision on Institution, and contends that "comprising" is a term of art in patent law, and not susceptible to the narrow construction proffered by UTC. Pet. Reply 21. SteadyMed also observes (*id.*) that UTC argued in its Preliminary Response for broadly construing that term to mean "including but not limited to" (Prelim. Resp. 23). SteadyMed further asserts that UTC fails to identify any statements in the prosecution history regarding the meaning of "comprising," and improperly conflates the examiner's allowance of the challenged claims with a disavowal of claim scope. Pet. Reply 21.

SteadyMed additionally argues that the interpretation of "comprising" proffered by UTC cannot effect UTC's desired result of limiting the challenged claims to require a particular impurity profile. SteadyMed asserts that the record is devoid of support for the conclusion that the claimed products and recited processes have unique impurity profiles. *Id*. at 22. In this regard, SteadyMed contends that the observed impurity profiles are not unique to the challenged claims, but rather, depend on unclaimed elements like what solvents were used, whether intermediate products were purified, and what bases, acids, or other reactants were used (*id*. at 23).

"In the patent claim context the term 'comprising' is well understood to mean 'including but not limited to.'" *CIAS, Inc. v. Alliance Gaming Corp.*, 504 F.3d 1356, 1360 (Fed. Cir. 2007); *see also Genentech, Inc. v. Chiron Corp*., 112 F.3d 495, 501 (Fed. Cir. 1997) ("'Comprising'

is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim."). Moreover, the specification of the '393 patent itself adopts this art-established definition of "comprising," stating "[t]he expression 'comprising' means 'including but not limited to.' Thus, other non-mentioned substances, additives, carriers, or steps may be present." Ex. 1001, 4:23–25.

Indeed, in its Preliminary Response, UTC noted both that "comprising" is a term of art in patent law, and that the specification of the '393 patent defines "comprising" consistently with its well-understood meaning in arguing that the claim term "[a/the] process comprising" should be construed to mean "a/the process including but not limited to." Prelim. Resp. 23–24. In contrast, UTC does not identify, and we do not discern support in either the specification or the prosecution history for the proposition that the Applicant disclaimed or disavowed the full scope of "comprising."

Accordingly, upon review of the parties' arguments and the evidence before us, including the claims, specification, and prosecution history of the '393 patent, we conclude that the broadest reasonable interpretation of the term "comprising," as it is used in the '393 patent, is "including, but not limited to."

b. "Product"

UTC asserts that both the specification and prosecution history of the '393 patent demonstrate that the product of the challenged claims must have the particular impurity profile that is conferred by the

recited process steps (PO Resp. 17), and, thus, the challenged claims exclude products made using different processes, such as the process taught by Moriarty (*id*. at 16). UTC further argues that "product" should be construed as "a substance resulting from a chemical reaction." *Id*. at 17.

SteadyMed agrees with our determination in the Decision on Institution that the term "product," as it is used in the '393 patent, does not require interpretation because the claimed "product" is defined by the limitations recited in the challenged claims. Pet. Reply 21. In this regard, SteadyMed points out that UTC's expert, Dr. Williams, contemplates four different meanings for that term, only one of which conforms to the narrow interpretation advanced by UTC. *Id*. at 21–22.

SteadyMed additionally asserts that UTC's proffered interpretation of "product" cannot effect the desired result of limiting the challenged claims to require a particular impurity profile. SteadyMed argues that the record is devoid of support for the conclusion that that claimed processes and their products have unique impurity profiles. *Id*. at 22. In this regard, SteadyMed contends that the observed impurity profiles are not unique to the challenged claims, but rather, depend on unclaimed elements like what solvents were used, whether intermediate products were purified, and what bases, acids, or other reactants were used. *Id*. at 23.

In patent parlance, "product" claims relate to structural entities, i.e., compositions of matter, machines, and manufactures. 1 DONALD S. CHISUM, CHISUM ON PATENTS, § 1.02 (Matthew Bender, 2017)

("Three of the four classes of statutory subject matter of utility patents (machines, manufactures, and compositions of matter) relate to structural entities and can be grouped as 'product' claims in order to contrast them with process claims."); *see also* MPEP § 2103 (9th ed., Rev. 07.2015, November 2015) ("Product claims are claims that are directed to either machines, manufactures or compositions of matter."). Accordingly, "[f]or products, the claim limitations will define discrete physical structures or materials." MPEP § 2103.

That a product is claimed in product-by-process format does not support deviation from this rule. Indeed, to subsume evaluation of whether the process steps recited in the challenged claims distinguish the claimed product from the prior art into the claim construction analysis, as UTC suggests, would be to improperly conflate the claim construction determination and patentability analysis, and would require importing unrecited limitations into the claims. As our reviewing court has explained:

> "In determining validity of a product-by-process claim, the focus is on the product and not the process of making it." *Amgen Inc. v. F. Hoffman–La Roche Ltd*., 580 F.3d 1340, 1369 (Fed.Cir.2009). . . . However, there is an exception to this general rule that the process by which the product is made is irrelevant. As we recognized in *Amgen*, if the process by which a product is made imparts "structural and functional differences" distinguishing the claimed product from the prior art, then those differences "are relevant as evidence of no

> anticipation" although they "are not explicitly part of the claim."

Greenliant Sys., Inc. v. Xicor LLC, 692 F.3d 1261, 1268 (Fed. Cir. 2012).

Even setting aside the art-established meaning of "product," UTC's proposed construction of that term as "a substance resulting from a chemical reaction," having the impurity profile conferred by performance of the recited process steps is unsupported by either the intrinsic or extrinsic evidence of record. Neither the specification nor the prosecution history of the '393 patent defines the term "product." In addition, the portions of the specification to which UTC points comport with an understanding of "product" as being defined only by the recited claim elements. For example, the bulk of the specification excerpts identified by UTC in its Patent Owner Response (PO Resp. 17) as supporting an interpretation of "product" as "a substance resulting from a chemical reaction" simply mirror the language of the process steps recited in the challenged claims, and do not further characterize the claim term "product." Ex. 1001, 3:3–4, 3:65–66, 6:65–66. Reference in the '393 patent specification to preparing the compound of formula II "from a compound of formula XI, which is a cyclization product of a compound of formula X" (*id*. at 7:17) likewise does not support UTC's proposed construction (PO Resp. 17). Indeed, if any conclusion can be drawn from the specification excerpts highlighted by UTC, it is that the claim term "product" is defined solely by the recited claim limitations. *See* Ex. 1001, 5:45–46 (referring to the purportedly improved impurity of the

"product of the process according to the present invention.").

Moreover, as UTC's expert, Dr. Williams explains, "chemists use the word 'product' in two different contexts, routinely." Ex. 2059, 248:4–5. "[T]here's the molecular structural context, and then there's the real-world substance context of the word 'product.'" *Id*. at 248:19–21. Indeed, Dr. Williams' own writings indicate that the term "product" does not necessarily refer to the result of a chemical reaction. Ex. 2020 ¶ 63 ("The scarcity of the natural product from marine sources renders Et-743 an important target for synthesis."). Accordingly, we do not agree with UTC that the broadest reasonable interpretation of "product" as used in the '393 patent includes a requirement that the claimed "product" be "a substance resulting from a chemical reaction."

Nor do we agree with UTC (PO Resp. 17) that the specification or prosecution history of the '393 patent disclaims or disavows from the scope of the term "product" substances having a different overall purity, or different impurity profile than is purportedly conferred by the recited process steps. "While a court may look to the specification and prosecution history to interpret what a patentee meant by a word or phrase in a claim, extraneous limitations cannot be read into the claims from the specification or prosecution history." *Bayer AG. v. Biovail Corp.*, 279 F.3d 1340, 1348 (Fed. Cir. 2002).

During prosecution of the '393 patent, relying on the Declaration of Dr. David Walsh ("Walsh Declaration"), the applicants argued that "the product of present claims is physically differen[t] than treprostinil

produced according to the process of Moriarty," and, therefore, "Moriarty cannot anticipate the present claims." Ex. 1002, 344. In his declaration, Dr. Walsh presented a comparison of three certificates of analysis, one for each of treprostinil free acid prepared according to Moriarty, treprostinil diethanolamine prepared according to challenged claims 1 or 9, and treprostinil free acid prepared according to challenged claims 1 or 9.[10] *Id*. at 347–349. Dr. Walsh went on to testify that the treprostinil of Moriarty was physically different from treprostinil prepared according to challenged claims 1 or 9 because the former included detectable amounts of certain impurities not observed in the latter. *Id*. at 349. The examiner subsequently issued a Notice of Allowance. *Id*. at 354–360.

The applicants' arguments during prosecution concerning the alleged physical differences between treprostinil prepared according to Moriarty and treprostinil prepared according to the process steps recited in the challenged claims are not tantamount to a clear disclaimer or disavowal of the full scope of the claim term "product." As an initial matter, the applicants did not identify a specific impurity profile associated with treprostinil produced according to the recited process steps that could serve as a definite limitation on claim scope; rather, the applicants simply asserted that the Moriarty treprostinil was physically different from that made according to the '393 patent (Ex. 1002, 344). Moreover, the certificates of analysis for treprostinil diethanolamine and treprostinil free

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[10] Issued claim 9 of the '393 patent is identified as claim 10 in the Walsh Declaration, and other documents in the prosecution history in the '393 patent.

acid presented in the Walsh Declaration indicate that treprostinil compounds produced according to the challenged claims can have different impurity profiles and purity levels, suggesting that an attempt to define such parameters would prove elusive. Ex. 1002, 348. Indeed, as discussed in greater detail in Parts II.C.2.b, II.D.2.e, and II.E.3.d., below, the evidence of record establishes that the variability in the impurity profile and overall purity level between individual batches of treprostinil produced according to the process steps recited in the challenged claims renders the claimed treprostinil structurally and functionally the same as treprostinil produced according to Moriarty. In addition, even assuming Dr. Walsh's analysis of the impurity profiles for treprostinil produced according to Moriarty and the '393 patent is correct, the prosecution history is devoid of evidence to support the conclusion that those differences are due to the recited process steps themselves, and not the use of unclaimed reagents and reaction conditions, or that any differences in impurity profile extend to the thousands of additional compounds covered by the challenged claims.

The specification of the '393 patent likewise does not disclaim or disavow the full scope of the term "product." Akin to its arguments concerning the prosecution history of the '393 patent, UTC does not specifically identify the contours of the subject matter purportedly disavowed or disclaimed by the specification. In addition, although UTC points to Example 6 of the '393 patent specification, and the related discussion, as supporting the conclusion that "the claimed 'product' must have an impurity profile conferred by its process steps" (PO Resp. 17), UTC does

not identify, and we do not discern discussion in the specification of the impurity profile for treprostinil prepared either by the recited process, or as described by Moriarty.

Example 6 of the specification presents a comparison of processes for preparing treprostinil according to Moriarty and a working example of the process disclosed in the '393 patent. Ex. 1001, 15:1–17:26. Example 6 reports an overall purity of ~99.0% for Moriarty treprostinil, and one of 99.9% for treprostinil prepared in accordance with the claimed invention. Example 6 does not disclose the impurity profile for treprostinil made by either process.

In describing Example 6, the specification states:

> The quality of treprostinil produced according to this invention is excellent. The purification of benzindene nitrile by column chromatography is eliminated. The impurities carried over from intermediate steps (i.e. alkylation of triol and hydrolysis of benzindene nitrile) are removed during the carbon treatment and the salt formation step. Additional advantages of this process are: (a) crude treprostinil salts can be stored as raw material at ambient temperature and can be converted to treprostinil by simple acidification with diluted hydrochloric acid, and (b) the treprostinil salts can be synthesized from the solution of treprostinil without isolation. This process provides better quality of final product

> as well as saves significant amount of solvents and manpower in purification of intermediates.

Id. at 17:27–40.

Neither the purported difference in overall purity of treprostinil produced according to Moriarty versus that produced according to the process of the '393 patent, nor stated advantages of the '393 patent process as compared to the Moriarty process constitutes a disavowal or disclaimer of the full scope of the term "product." Example 6 includes numerous process steps in addition to those recited in the challenged claims, and it is not apparent from the specification that the reported purity improvement over Moriarty treprostinil is due to the recited process steps, rather than the unclaimed steps. Furthermore, as Dr. Williams testifies, "there is the possibility for significant batch-to-batch variations in the impurity profile of each batch of treprostinil." Ex. 2020 ¶ 93 (internal quotation omitted). In addition, as discussed in greater detail in Parts II.C.2.b., II.D.2.e., and II.E.3.d., below, the overall purity for Moriarty treprostinil set forth in the '393 patent specification is inconsistent with that reported by Moriarty (99.7%) (Ex. 1004, 13), as well as the average purity of 46 commercial Moriarty batches (99.7%) (Ex. 1021; Ex. 2059, 218:3–219:20). Lastly, we observe that the challenged claims contain no limitations relating to the impurity profile of the recited product, "and it is the claims ultimately that define the invention." *Purdue Pharma L.P. v. Endo Pharm. Inc.*, 438 F.3d 1123, 1136 (Fed. Cir. 2006).

Accordingly, upon review of the parties' arguments and the evidence before us, including the claims, specification, and prosecution history of the '393

patent, we conclude that the term "product," as it is used in that patent, does not require construction because the claimed "product" is defined by the limitations recited in the challenged claims. We additionally conclude that the broadest reasonable construction of the larger phrase "[a] product comprising a compound [of/having] formula [I/IV] . . . or a pharmaceutically acceptable salt thereof" is "a product including, but not limited to, a compound [of/having] formula [I/IV] or a pharmaceutically acceptable salt thereof."

2. "[A/the] process comprising"

Claims 1 and 9 recite "[a/the] process comprising." In the Decision on Institution, we construed this term to mean "a/the process including, but not limited to." Dec. 13. Neither SteadyMed nor UTC challenges the interpretation set forth in the Decision on Institution. *See* PO Resp. 13–18; Pet. Reply 21–23. Accordingly, for the reasons set forth in the Decision on Institution (Dec. 13), we broadly, but reasonably, construe "[a/the] process comprising" to mean "a/the process including, but not limited to."

B. Principles of Law

To establish anticipation, each and every element in a claim, arranged as recited in the claim, must be found in a single prior art reference. *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008). "A reference anticipates a claim if it discloses the claimed invention 'such that a skilled artisan could take its teachings in combination with his own knowledge of the particular art and be in possession of the invention.'" *In re Graves*, 69 F.3d 1147, 1152 (Fed.

Cir. 1995) (emphasis omitted) (quoting *In re LeGrice*, 301 F.2d 929, 936 (CCPA 1962)).

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *KSR Int'l Co. v. Teleflex Inc*., 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

> When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill. *Sakraida* [*v. Ag Pro, Inc*., 425 U.S. 273 (1976)] and *Anderson's–Black Rock* [*v. Pavement Salvage Co*., 396 U.S. 57 (1969)] are illustrative—a court must ask whether the improvement is more

> than the predictable use of prior art elements according to their established functions.

KSR, 550 U.S. at 417.

The level of ordinary skill in the art may be reflected by the prior art of record. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001); *In re GPAC Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995); *In re Oelrich*, 579 F.2d 86, 91 (CCPA 1978).

"The objective indicia of non-obviousness play an important role as a guard against the statutorily proscribed hindsight reasoning in the obviousness analysis." *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1328 (Fed. Cir. 2016). Indeed, "evidence of secondary considerations may often be the most probative and cogent evidence [of nonobviousness] in the record." *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983).

C. Anticipation Grounds of Unpatentability Based on Phares

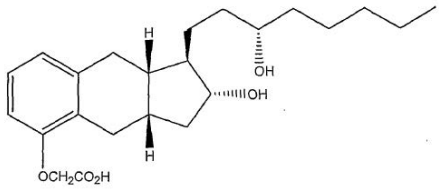
SteadyMed asserts that claims 1–5, 7–9, 11–14, and 16–20 are unpatentable under § 102(b) as anticipated by Phares. Pet. 22–37. Claims 2–5, 7, 8, and 19 depend directly from claim 1, and claims 11–14, 16–18, and 20 depend, directly or indirectly, from claim 9. In support of its assertion, SteadyMed provides detailed explanations as to how Phares discloses each claim limitation (*id.*), and relies upon the Winkler Declaration (Ex. 1009) and the Rogers Declaration (Ex. 1022) to support its positions.

Upon review of SteadyMed's contentions and supporting evidence, as well as UTC's Patent Owner

Response and supporting evidence, we determine that SteadyMed has demonstrated, by a preponderance of the evidence, that claims 1–5, 7–9, 11–14, and 16–20 of the '393 patent are unpatentable over Phares.

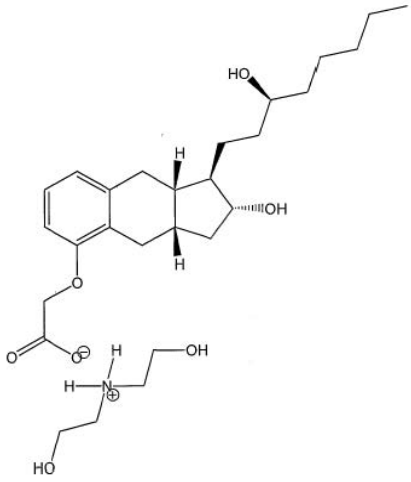
1. Phares

Phares describes "compounds and methods for inducing prostacyclin-like effects in a subject or patient," including treprostinil and derivatives thereof. Ex. 1005, 10. The chemical structure of treprostinil disclosed by Phares, on page 10 of Exhibit 1005, is reproduced below:



Id. Phares explains that "[t]reprostinil is a chemically stable analog of prostacyclin, and as such is a potent vasodilator and inhibitor of platelet aggregation." *Id*.

Phares further discloses that "[a] preferred embodiment of the present invention is the diethanolamine salt of treprostinil . . . . A particularly preferred embodiment of the present invention is form B of treprostinil diethanolamine." *Id*. at 11. The structure of the diethanolamine salt of treprostinil described by Phares, on page 99 of Exhibit 1005, is reproduced below:



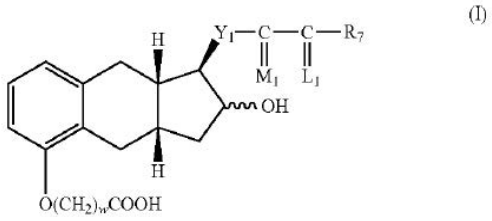
Id. at 99 (claim 49). Phares reports that form B of the diethanolamine salt of treprostinil "appears to be a crystalline material which melts at 107°C." *Id*. at 91.

Phares describes the synthesis of (-)-treprostinil, the enantiomer of treprostinil. Ex. 1005, 41–42. Phares explains that "[e]nantiomers of these compounds . . . can be synthesized using reagents and synthons of enantiomeric chirality of the above reagents." *Id*. at 41. In particular, Phares teaches that "the enantiomer of the commercial drug (+)-Treprostinil was synthesized using the stereoselective intramolecular Pauson Khand reaction as a key step and Mitsunobu inversion of the side-chain hydroxyl group." *Id*. at 42. Phares discloses the following reaction procedure: "i. $ClCH_2CN$, K_2CO_3. ii, KOH, CH_3OH, reflux. 83 % (2 steps)." *Id*.

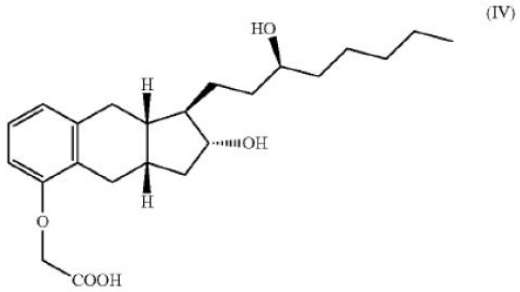
2. Discussion

Each of the challenged claims, including independent claims 1 and 9, is a product-by-process

claim. Claim 1 of the '393 patent recites "[a] product comprising a compound of formula I



or a pharmaceutically acceptable salt thereof," and sets forth a series of process steps for obtaining the claimed product. Claim 9 recites "[a] product comprising a compound having formula IV



or a pharmaceutically acceptable salt thereof," and includes the same process steps for obtaining the claimed product as recited in claim 1.

Claim 9 is identical to claim 1, except that it is drawn to a product comprising the specific treprostinil compound, a species of the genus of claim 1. Accordingly, we address claims 1 and 9 together. Dependent claim 2 further limits claim 1, additionally requiring that "the purity of compound of formula I in said product is at least 99.5%."

SteadyMed contends that "Phares discloses in its Claim 49 the identical, pharmaceutically acceptable treprostinil diethanolamine salt" claimed in the '393 patent. Pet. 26. SteadyMed further asserts that the process steps recited in the challenged claims of the '393 patent do not result in a treprostinil product that is physically different or unique from treprostinil produced by prior art methods. *Id*. at 19–22. In support of its position, SteadyMed argues that because the melting point for treprostinil diethanolamine salt reported by Phares is higher and exhibits a narrow range than that reported in the '393 patent, the treprostinil diethanolamine salt of Phares is at least as pure as that generated according to the process of the '393 patent. *Id*. at 27–28. SteadyMed also asserts that Phares inherently anticipates the process steps recited in the challenged claims. *Id*. at 24–28.

We have reviewed the Petition and the supporting evidence to which we are directed as to how Phares teaches each limitation of the challenged claims. We are persuaded by SteadyMed's showing that Phares discloses the identical, pharmaceutically acceptable treprostinil diethanolamine salt claimed in the '393 patent. Ex. 1005, 99 (claim 49); *see also* Ex. 1009 ¶¶ 52–53.

Notwithstanding UTC's arguments to the contrary, which we address below, we are also persuaded by SteadyMed's showing that the process steps recited in the challenged claims of the '393 patent are not entitled to patentable weight because they do not result in a treprostinil product that is structurally or functionally different from treprostinil produced by prior art methods. In this regard, we note, as SteadyMed points

out, that the 99.7% treprostinil purity reported by Moriarty (Ex. 1004, 13) exceeds each of the purity levels exemplified in the specification of the '393 patent (Ex. 1001, 8:66–67), as well as the 99.5% purity recited in dependent claims 2 and 10 of the '393 patent, the only challenged claims that recite a purity level (*id*. at 19:30–31, 20:47–48). Pet. 20–21. Moreover, as discussed in greater detail below, we are persuaded by SteadyMed's showing that any purported differences in the overall purity or impurity profile observed for treprostinil produced according to the '393 patent as compared to prior art methods are attributable to inter-batch variability in purity levels and impurity profiles, as well as variations in reagents, solvents, and reaction conditions, rather than structural and functional differences arising from performance of the process steps recited in the challenged claims. *Id*. at 21.

UTC does not dispute that Phares discloses the identical chemical structure for the treprostinil diethanolamine product claimed in the '393 patent. UTC asserts, however, that SteadyMed improperly combines disparate disclosures of Phares in arguing that Phares teaches the same process for manufacturing treprostinil as recited in claims 1 and 9. PO Resp. 19–20, 24–26.

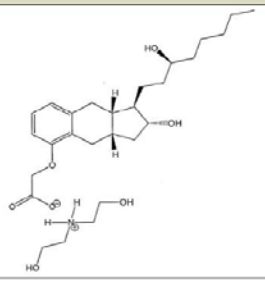
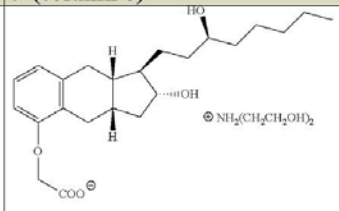
Corollary to its contentions concerning how Phares treprostinil is made, UTC additionally argues that treprostinil produced according to Phares exhibits differences in overall purity and impurity profile compared to treprostinil produced according to the challenged claims, and, thus, cannot anticipate the claimed product. *Id*. at 20–26. In this regard, UTC argues that "SteadyMed must show that the Phares'

diethanolamine salt necessarily possesses an impurity profile that is distinct from that of the Moriarty product and with higher purity." *Id*. at 21. UTC further asserts that the melting point data on which SteadyMed relies as establishing that Phares treprostinil is of at least equal purity to treprostinil produced according to the recited process is "not necessarily a reliable metric of purity" (*id*. at 22), and that SteadyMed's analysis of Phares' purity level is unsound (*id*. at 23–24). With regard to dependent claim 2, UTC argues that "nothing in Phares discloses a purity of at least 99.5%." *Id*. at 24.

Lastly, UTC asserts that "[b]ecause Phares does not disclose the process of preparing the starting treprostinil acid for the diethanolamine salt, the impurity profile of the diethanolamine salt cannot be established" and, thus, SteadyMed "cannot show that it is necessarily identical to the claimed product or has equal purity to the claimed product." *Id*. at 26. We address UTC's arguments below.

a. "A product comprising a compound [of/having] formula [I/IV] . . . or a pharmaceutically acceptable salt thereof"

It is undisputed that Phares and the '393 patent disclose identical chemical structures for treprostinil diethanolamine salt. This structural identity is illustrated in the side-by-side comparison of the compounds disclosed in claim 49 of Phares, and column 8, lines 50–63 of the '393 patent set forth in paragraph 52 of the Winkler Declaration, and reproduced below:

Phares (Ex. 1005), Claim 49	'393 Patent (Ex. 1001), Claims 1 & 9 (column 8)
	

Ex 1009 ¶ 52. As shown in the figure from paragraph 52 of the Winkler Declaration, the treprostinil diethanolamine salt disclosed by Phares is structurally identical to that disclosed in the '393 patent.

b. Recited Process Steps

In order to determine whether Phares anticipates the challenged claims, we must determine whether the process steps recited in the challenged product-by-process claims are entitled to patentable weight. The general rule when determining patentability of a product-by-process claim is to "focus . . . on the product and not on the process of making it." *Amgen, Inc. v. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1369 (Fed. Cir. 2009). This rule embodies the long-standing principle that "an old product is not patentable even if it is made by a new process." *Id*. at 1370. Thus, although a party may be entitled to a patent on a method for purifying a known substance, it is "not entitled to a patent on the article which after being produced has a greater degree of purity than the product produced by former methods." *In re Merz*, 97 F.2d 599, 601 (CCPA 1938).

An exception to the general rule applies, however, when process steps recited in the claim impart

"structural and functional differences" to the claimed product. *Greenliant Sys.*, 692 F.3d at 1267–1268. If the exception applies, the structural and functional differences conveyed by the recited process steps "'are relevant as evidence of no anticipation' although they 'are not explicitly part of the claim.'" *Id*. at 1268 (citing *Amgen*, 580 F.3d at 1370); *Merz*, 97 F.2d at 601 ("[I]f the process produces an article of such purity that it differs not only in degree but in kind it may be patentable.").

Based on the entire record before us, we find that the process steps recited in the challenged claims do not impart structural or functional differences to the claimed product, and, therefore, conclude that those process steps are not entitled to patentable weight. Instead, we find that the evidence of record supports a finding that treprostinil produced according to Phares has the same, or better, overall purity and purity profile than treprostinil produced according to the process recited in the '393 patent. We further find that, to the extent they exist at all, any purity differences between treprostinil produced by prior art methods and that produced according to the process recited in the '393 patent are attributable to inter-batch variability in impurity profiles, as well as variations in reagents, solvents, and reaction conditions, and are not indicative of structural or functional differences imparted by performing the steps recited in the challenged claims of the '393 patent. Moreover, even assuming the existence of impurity differences between prior art treprostinil and '393 patent treprostinil, we find that the evidence of record does not support a determination that those impurity differences render

prior art treprostinil functionally different from '393 patent treprostinil.[11]

As an initial matter, we observe that UTC does not identify, and we do not discern, evidence of record to suggest that treprostinil produced according to the process steps recited in claims 1 and 9 has a higher overall purity or different impurity profile than treprostinil diethanolamine salt produced according to Phares. Although UTC attempts to discredit evidence proffered by SteadyMed to demonstrate that Phares treprostinil is of equivalent purity to that produced according to the '393 patent (which arguments we address below), it is nevertheless the case that the record is devoid of evidence affirmatively suggesting the existence of any structural or functional difference between treprostinil made according to Phares and that made according to the '393 patent.

Moreover, we find that the 107°C melting point for treprostinil diethanolamine salt Form B reported by Phares (Ex. 1005, 91) indicates that the treprostinil product produced by to Phares is at least as pure as that made according to the steps recited in the '393 patent. Phares and the '393 patent each report melting point data for treprostinil diethanolamine salt Form B. Ex. 1005, 91; Ex. 1001, 12:52–13:20, 13:50–65. In particular, Phares reports a melting point of 107°C (Ex. 1005, 91), and the '393 patent reports melting point ranges of 104.3°C–106.3°C, 105.5°C–107.2°C,

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[11] Because we determine that the recited process steps are not entitled to patentable weight, we do not address the parties' contentions concerning Phares' anticipation of the recited process steps.

104.7°C–106.6°C, 105°C–108°C, 105.0°C–106.5°C, and 104.5°C–105.5°C (Ex. 1001, 12:52–13:20, 13:50–65). Because the melting point for treprostinil diethanolamine salt Form B produced according to Phares exceeds the melting point ranges reported for four batches produced according to the challenged claims, and falls within the ranges of the remaining two batches, we find that the treprostinil diethanolamine salt produced according to Phares is of at least equal purity to that produced by the recited process steps, and thus, is not structurally or functionally different from '393 patent treprostinil. We also find that the 2°C width of the melting peak for treprostinil diethanolamine salt Form B reported by Phares further indicates a high purity for Phares treprostinil, although we note that this additional finding is not essential to our determination that Phares treprostinil is not structurally or functionally different from treprostinil produced according to the '393 patent. Ex. 1005, Fig. 21.

In making these findings, we credit the testimony of SteadyMed's polymorph expert, Dr. Rogers that "[n]o matter how Form B is made, Form B has a single, defined melting point. If impurities are present, the apparent melting point may decrease due to a phenomenon called 'melting point depression,' but the melting point of a pure substance never changes." Ex. 1022 ¶ 64. In this regard, we note that reliance by Dr. Williams, UTC's expert, on Adhiyaman[12] as suggesting

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[12] R. Adhiyaman and Sanat Kumar Basu, *Crystal Modification of Dipyridamole Using Different Solvents and Crystallization Conditions*, Int'l J. Pharmaceutics 321:27-34 (2006) ("Adhiyaman") (Ex. 2030).

that two crystals having the same crystal form could have different pure melting point ("T_0") values if made using different solvents (*see* Ex. 2022 ¶ 75) is misplaced. As explained by Dr. Rogers (Ex. 1022 ¶¶ 78–80), in Adhiyaman, different crystal forms of the same drug were made using different solvents, and thus, the different crystal forms exhibited different pure melting points. Ex. 2030, 4–5; *see also* Ex. 2059, 180:9–25. In contrast, Phares and the '393 patent discuss the same crystal form—treprostinil diethanolamine salt Form B—and, accordingly, "the crystals being compared in the '393 Patent and Phares Reference are the same crystal form, and thus have the same T_0 pure melting point value. Any difference in their measured melting point, T_s, is due to differing levels of impurities." Ex. 1022 ¶ 82. Because it is consistent with the disclosures of Phares, we also credit Dr. Roger's testimony that the onset temperature for Phares' treprostinil diethanolamine salt Form B is 105.00°C, and, therefore, the width of the melting peak reported by Phares is 2°C, suggesting a high overall purity level. Ex. 1022 ¶ 87; *see also* Ex. 1005, Fig. 21.

We also find unpersuasive UTC's contention that the melting point data provided in Phares is insufficient to support a determination that treprostinil produced according to Phares is of equivalent purity to that produced according to the '393 patent. PO Resp. 22, 25–26. In this regard, we note that neither UTC nor Dr. Williams identifies support for Dr. Williams' opinion that an ordinarily skilled artisan "would not have concluded based on a single melting point example of polymorph B prepared under unknown conditions (e.g., recrystallization solvent and recrystallization conditions are not identified) would be

of a higher purity than the known purity of the '393 patent" (Ex. 2020 ¶ 76; *see also id*. ¶¶ 77–78). We are similarly unpersuaded by Dr. Williams' conclusory testimony that the purity values reported in Phares and the '393 patent cannot be compared because "[i]t is known in the art that sample size, rate of heating, the recrystallization solvent(s) used, and the conditions under which the crystalline sample was obtained can significantly affect the DSC data" (*id*. ¶ 76; *see also id*. ¶¶ 77–78), as well as his generic assertion, unsupported by reference to scientific literature, that in his experience, crystals having the same crystal form but made with different solvents can exhibit different pure melt points (*see* Ex. 2059, 184:22–185:2). We give such testimony little or no weight. 37 C.F.R. § 42.65(a).

Furthermore, as Dr. Williams' acknowledges, he is "not a polymorph expert." Ex. 2059, 158:17–18; *see also id*. at 156:25–157:2. In addition, the record nowhere indicates that Dr. Williams' experience with identical crystal forms made using different solvents exhibiting different pure melting points extends to treprostinil or related compounds. We are also unpersuaded by Dr. Williams' opinion that Phares' treprostinil diethanolamine salt exhibits a "broad melting peak with a range of close to 10 degrees which is indicative of a lower purity substance" (Ex. 2020 ¶ 76). In particular, we note that Dr. Williams does not explain how he determined the width of that peak, or how the peak width he identified relates to the onset of the melting event. *See id*.

Neither do we agree with UTC's contention that "SteadyMed must show that the Phares' diethanolamine salt necessarily possesses an impurity

profile that is distinct from that of the Moriarty product and with higher purity." PO Resp. 21. In order for process steps recited in a product-by-process claim to be entitled to patentable weight, they must impart structural and functional differences onto the product claimed. *See Greenliant*, 692 F.3d at 1267–1268. Accordingly, the relevant comparison is between Phares treprostinil and '393 patent treprostinil, irrespective of what starting materials were used by Phares. As explained above, the evidence of record shows that Phares treprostinil is of at least equal purity to '393 patent treprostinil, and, therefore, treprostinil produced according to the process steps recited in the challenged claims cannot be said to differ structurally or functionally from treprostinil produced according to Phares.

Although UTC does not endeavor to compare the purity of Phares' treprostinil to that produced according to the '393 patent, it does present purity data for developmental and commercial batches of '393 patent treprostinil, as well as for treprostinil purportedly made according to the process described by Moriarty (Ex. 2020, Appx. A–B (compiling purity data); Ex. 2059, 79:11–16, 81:14–22 (identifying first ten batches of Appendix A as development batches); *id*. at 272:15–273:16 (identifying first five batches of Appendix B as development batches)), which SteadyMed contends would have been the starting material used by Phares (Pet. 25–26). The average overall purity as measured by HPLC for the commercial batches of '393 patent treprostinil and for the commercial batches of Moriarty treprostinil is the same: 99.7%. Ex. 2059, 218:25–219:20; *see also id*. at 93:11–25; Ex. 1021. Notably, this is the same HPLC

purity assay value as reported by Moriarty. Ex. 1004, 13 (reporting an HPLC-determined "purity [of] 99.7%", and noting that the compound tested "was identical in all respects to an authentic sample of UT-15 [treprostinil]").[13]

Because UTC's expert, Dr. Williams, included a disproportionate number of development batches relative to commercial batches in its overall purity calculation for Moriarty treprostinil (10 development batches out of a total of 56 batches) (*see* Ex. 2059, 79:11–16, 81:14–22) as compared to '393 patent treprostinil (5 development batches out of a total of 121) (*see id*. at 272:15–273:16), and did not account for this disparity in the purity calculation, we find that the comparison of like to like, as represented by the average overall purity of the commercial batches only, provides the most reliable evidence of treprostinil purity. We also find that the development batches are a less reliable indicator of product purity, as they are not necessarily representative of the final, fully optimized production processes. *See e.g.*, Ex. 2059 102:9–12 ("So the development batches for the '393 are also poorer than the later commercial batches. And so by the same token, those numbers bring down the average purity of the '393 process."), 102:20–22 ("But if

[13] UTC urges us to ignore the purity reported by Moriarty because "it is not clear what method was used to determine the purity in Moriarty." PO Resp. 29. We observe, however, that Moriarty, like the '393 patent specification itself, discloses that an HPLC purity assay was used without identifying the particular reference standard employed. We further note that because reference standards are just that, the absence of information concerning the precise reference standard used does not call into question the validity of the purity reported in Moriarty.

you did eliminate the development batches, it would certainly improve the overall purity of the '393 batches."), 105:11–16 ("[W]ith the — the Moriarty process, you're starting with an inferior process. So the development batches were not as nice as the development batches that you started with the '393. . . .").

As further support for these findings, we observe that Dr. Williams neither asserts that exclusion of the development batches from the purity analysis would be improper (*see, e.g.*, Ex. 2059, 91:12–20, 115:7–18), nor articulates any reason the development batches should be included in the purity analysis, beyond stating that he included development batches for both processes and factored all of the data that was presented to him into his calculation (*id*. at 271:25–272:5, 273:13–24). In addition, although it is not necessary to our findings, we note that Dr. Williams' uncertainty regarding whether the purported Moriarty development batches were in fact produced according to the Moriarty process provides an additional reason to exclude the alleged Moriarty development batches from the overall purity calculation. *See, e.g.*, Ex. 2059, 270:23–271:2. Accordingly, we find that there is no difference in the overall purity for treprostinil produced according to Moriarty and that produced according to the '393 patent.

UTC additionally argues that treprostinil produced according to the '393 patent has a different impurity profile than that produced by Moriarty. In particular, UTC contends that comparison of the average impurity profiles for treprostinil produced by each of these methods reveals that certain specific impurities found

in Moriarty treprostinil are essentially eliminated from treprostinil made according to the '393 patent. For example, UTC identifies three impurities as being eliminated from commercial batches of '393 patent treprostinil: 97W86, 1AU90, and 2AU90, and asserts that four more impurities are, on average, greatly reduced: methyl ester, 751W93, 750W93, and 3AU90. PO Resp. 10. UTC additionally states that ethyl ester is slightly increased in '393 patent treprostinil. *Id*. UTC then concludes that these impurity differences constitute structural differences between Moriarty and the claimed product.

But we find that UTC's reliance on average impurity profiles for treprostinil produced by different methods is misplaced, as UTC's averages do not account for the significant inter-batch variation in both the types and amounts of impurities present in batches of treprostinil made by either the Moriarty or the '393 patent process. *See, e.g.*, Ex. 2020, Appx. A–B (compiling impurity data from individual treprostinil batches); PO Resp. 11 ("Moriarty treprostinil may show inter-batch variation in overall purity and impurity profiles"); Ex. 2020 ¶ 93 ("Third, as Dr. Winkler himself points out, there is the possibility for 'significant batch-to-batch variations in the impurity profile of each batch of treprostinil.'"). We also find that the impurity profile averages on which Dr. Williams relies in asserting the existence of impurity differences between '393 patent treprostinil and Moriarty treprostinil are unpersuasive, because those averages obfuscate, and make no attempt to account for, the extent of inter-batch variation for treprostinil produced by any method.

The extent of the inter-batch variation for both Moriarty and '393 patent treprostinil batches is illustrated by the fact that, irrespective of the averages calculated by Dr. Williams, individual commercial batches of Moriarty treprostinil exhibit impurity profiles nearly identical, if not superior, to those seen in individual commercial batches of '393 patent treprostinil. For example, the table below compares the types and amounts of impurities detected in one commercial batch of Moriarty treprostinil (Lot. No. UT15-031202, Ex. 2036, 5) to those detected in one commercial batch of '393 patent treprostinil (Lot. No. 01F08017, Ex. 2037, 58–59).

Compound	**Moriarty UT15-031202 (Ex. 2036, 5)**	**'393 Patent 01F08017 (Ex. 2037, 58–59)**
1AU90	Not detected	Not detected
2AU90	Not detected	Not detected
97W86	Not detected	Not detected
3AU90	0.2%	0.09%
treprostinil methyl ester	<0.05%	<0.05%
treprostinil ethyl ester	0.2%	0.5%
750W93	0.07%	0.09%
751W93	<0.05%	<0.05%
unidentified impurities	Not detected	0.08%
total related substances	0.5%	0.8%
assay purity	99.7%	99.5%

As revealed by the above comparison, the Moriarty batch has a higher overall purity, and the same or lower amounts of all but one impurity, 3AU90, than the '393 patent batch. *Compare* Ex. 2036, 5, *with* Ex. 2037, 58–59. In addition, we observe that both the Moriarty batch and the '393 patent batch satisfy the treprostinil drug specification requirements concerning the types and amounts of impurities that may be present in a batch of treprostinil—which requirements notably did not change when UTC switched over from producing treprostinil according to Moriarty to producing it using the process disclosed in the '393 patent. Ex. 2036, 5; Ex. 2037, 58–59; Ex. 2006, 5–6; Ex. 2003. We further note that both batches also satisfy the overall purity requirements under the revised treprostinil drug specification (Ex. 2006, 3–4; Ex. 2003).

As explained above in Part II.A.1.b., the comparisons of purity data for Moriarty and '393 patent treprostinil set forth in the Walsh Declaration and in the specification of the '393 patent itself similarly indicate that batch-to-batch variation, rather than any structural or functional difference between treprostinil products, accounts for the reported differences in overall purity and impurity profile.

UTC additionally contends that whether individual batches of Moriarty treprostinil satisfy the current FDA purity specification is not relevant to patentability. Rather, UTC asserts that "[t]he question for patentability is whether or not a given batch of *starting* Moriarty treprostinil (steps a and b of the '393 independent claims) will be physically changed when step (c) is performed *on that batch*." PO Resp. 11. But whether an intermediate, or even the final product of

the Moriarty process might be further purified when subject to step (c) of the challenged claims is not the test for determining whether the process steps recited in the challenged product-by-process claims are entitled to patentable weight. Instead, the question before us is whether the process for making treprostinil set forth in the challenged claims imparts structural or functional differences to the product claimed as compared to prior art processes for making the claimed product. *See Greenliant*, 692 F.3d at 1267–1268. For the reasons set forth above, and as exemplified by comparison of individual batches of Moriarty and '393 patent treprostinil, we determine that the process steps set recited in the challenged claims do not impart structural or functional differences on the product claimed. Moreover, we observe that none of the asserted grounds of unpatentability depends on Moriarty alone; rather, each asserted ground of unpatentability is based, in whole or in part, on Phares, which expressly discloses step (c) of the asserted claims, and yields a treprostinil product that is at least as pure as '393 patent treprostinil. As evident from the discussion above, the use of Moriarty treprostinil as the starting material for the purification disclosed by Phares would result in a treprostinil diethanolamine salt at least as pure as that disclosed by the '393 patent, and thus, a product that is not structurally or functionally different from that disclosed by the '393 patent.

Furthermore, even if it had been shown that treprostinil produced according to the '393 patent differed in overall purity and/or impurity profile from treprostinil produced according to prior art methods, the record nevertheless fails to support a determination

that those differences confer patentable weight to the process steps recited in the challenged claims. *See Merz*, 97 F.2d at 601 ("No new use is claimed for appellant's purified ultramarine. It is the same old ultramarine with the same old use though it may have brighter color and be more desirable as a pigment than formerly."). Indeed, as Dr. Williams acknowledged during deposition, with chromatography, as is used in Moriarty, it would be possible to purify treprostinil to "99.99999 percent" by purifying and re-purifying the product. Ex. 2059, 94:1–24.

UTC nevertheless contends that the FDA's approval of UTC's request for a change in the purity assay value for the treprostinil from a range of 97%–101% to a range of 98%–102% was a "major" change evidencing the functional importance of the purported difference in purity between Moriarty treprostinil and treprostinil made according to the '393 patent. PO Resp. 12. UTC argues also that FDA pharmaceutical batch testing requirements, and prohibition by the FDA of the sale for patient use of batches that fall outside of the relevant purity specification further illustrate the importance of the alleged purity improvements obtained using the process recited in the '393 patent. *Id*.

Absent from the record, however, is evidence to suggest that the 1% increase in the purity assay value for treprostinil produced according to the '393 patent, or the FDA's general requirements for pharmaceutical purity, demonstrates a functional difference between Moriarty treprostinil and '393 patent treprostinil. Instead, the record indicates that batches of Moriarty treprostinil satisfy the 98% minimum purity

requirement for treprostinil approved by the FDA, and could be sold to the public (Ex. 2058, 179:23–180:17). This is true irrespective of whether the overall purity level of 99.7% reported by Moriarty (Ex. 1004, 13), 99.05% reported by Dr. Williams (Ex. 2020 ¶ 98), or 99.7% as obtained when development batches are excluded from Dr. Williams' analysis (Ex. 1021; Ex. 2059, 218:3–20) is accepted, as each of these reported purity levels exceeds the 98% purity required by the FDA. In addition, we note that UTC's expert, Dr. Ruffolo confirmed during deposition that the 1% purity change sought by UTC and approved by the FDA did not itself constitute a "major" change to the treprostinil drug specification. Ex. 2058, 310:5–18. Finally, we observe that the record does not include evidence to suggest the existence of any clinical or safety differences between Moriarty treprostinil and treprostinil produced according to the '393 patent. *See, e.g.*, Ex. 2058, 257:22–258:9, 315:15–23; Ex. 2059, 47:3–13.

With regard to the purported differences in the impurity profiles for Moriarty treprostinil and '393 patent treprostinil, we additionally note that UTC did not seek, and the FDA did not impose, any changes to the types or amounts of impurities that may be present in treprostinil manufactured according to the '393 patent versus that made by the Moriarty process. Ex. 2006, 5–6; Ex. 2003. We observe also that the '393 patent itself does not discuss any of the individual impurities, or attribute any clinical relevance to the purported differences between Moriarty treprostinil and that made according to the '393 patent process.

Accordingly, on the record before us, we determine that the process steps recited in the challenged claims of '393 patent do not impart structural or functional differences to the claimed product, and thus, do not patentably limit the claimed product.

c. Claim 2

Claim 2 depends from claim 1 and further requires that "the purity of compound of formula I in said product is at least 99.5%."

UTC asserts that Phares does not anticipate claim 2, because "nothing in Phares discloses a purity of at least 99.5%." PO Resp. 24.

We do not agree. For the reasons set forth above, we find that Phares treprostinil is at least as pure as treprostinil produced according to the process disclosed in the '393 patent, and therefore, Phares necessarily discloses treprostinil having a purity of 99.5% or higher. Ex. 1009 ¶ 62. Furthermore, a claim to a degree of purity in and of itself does not render the claim patentable over the prior art. *In re Fink*, 62 F.2d 103, 104 (CCPA 1932) (affirming decision where purity of claimed product was merely a matter of degree and there was no reason to believe that prior art product would not be as pure).

3. Conclusion

UTC does not separately argue claims 3–5, 7, 8, 11–14, and 16–20. *See* PO Resp. 18–26. We have reviewed Petitioner's evidence and argument as to those claims, and, based on the evidence, find that Petitioner has established by a preponderance of the

evidence that those claims are anticipated by Phares. Pet. 30–32, 34–37.

For the foregoing reasons, therefore, we determine SteadyMed has demonstrated, by a preponderance of the evidence, that claims 1–5, 7–9, 11–14, and 16–20 are unpatentable under § 102(b) as anticipated by Phares.

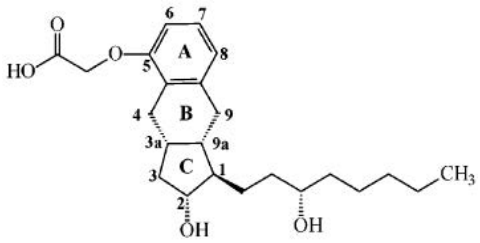
D. Obviousness Grounds of Unpatentability Based on Moriarty and Phares

SteadyMed asserts that claims 1–5, 7–9, 11–14, and 16–20 are unpatentable under § 103(a) as obvious in view of Moriarty and Phares. Pet. 37–52. In support of its assertion, SteadyMed provides detailed explanations as to how the combination of Moriarty and Phares discloses each claim limitation (*id*.), and relies upon the Winkler Declaration (Ex. 1009) and the Rogers Declaration (Ex. 1022) to support its positions.

Upon review of SteadyMed's contentions and supporting evidence, as well as UTC's Patent Owner Response and supporting evidence, we determine that SteadyMed has demonstrated, by a preponderance of the evidence, that claims 1–5, 7–9, 11–14, and 16–20 of the '393 patent are unpatentable over the combination of Moriarty and Phares.

1. Moriarty

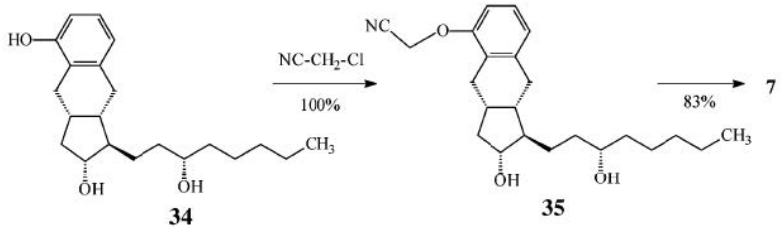
Moriarty describes the synthesis of treprostinil "via the stereoselective intramolecular Pauson-Khand cyclization." Ex. 1004, 1. Formula 7 of Moriarty is reproduced below:



7

Id. at 3. Formula 7 of Moriarty depicts the chemical structure of treprostinil. *Id*.

An excerpt of Scheme 4 of Moriarty is reproduced below:



34 35

Id. at 6. The excerpted portion of Scheme 4 of Moriarty illustrates the alkylation of Formula 34 to yield Formula 35, and subsequent hydrolysis of Formula 35 with a base (followed by acidification) to yield Formula 7, treprostinil. Ex. 1004, 6, 13.

2. Discussion

SteadyMed contends that Moriarty and Phares respectively disclose treprostinil acid and treprostinil diethanolamine salt, as recited in that challenged claims of the '393 patent. Pet. 22–23, 24, 33, 39, 48. SteadyMed further asserts that Moriarty discloses steps (a) and (b), and Phares discloses step (c) of the

process recited in independent claims 1 and 9 of the '393 patent. Pet. 43, 48–49.

We have reviewed the Petition and the supporting evidence to which we are directed as to how the combination of Moriarty and Phares discloses each limitation of the challenged claimed. We are persuaded by SteadyMed's showing that the combination of Moriarty and Phares discloses both the treprostinil products claims, as well as the production of those treprostinil products through the performance of steps (a)–(c) recited in claims 1 and 9 of the '393 patent.

Relying on its expert, Dr. Winkler, SteadyMed asserts that an ordinarily skilled artisan, at the time of invention of the '393 patent, would have had reason to combine, and a reasonable expectation of success in combining, Moriarty and Phares. Pet. 43. Dr. Winkler testifies that an ordinarily skilled artisan would have sought to combine Moriarty and Phares in order to eliminate the intermediate purification step taught by Moriarty, thereby increasing synthetic efficiency and lowering production costs for treprostinil diethanolamine salt. Ex. 1009 ¶¶ 77–78. Dr. Winkler additionally testifies that an ordinarily skilled artisan would have had a reasonable expectation of success in reacting treprostinil with diethanolamine because Phares successfully performed precisely that reaction. *Id*. ¶ 80.

Notwithstanding UTC's arguments to the contrary, which we address below, we are persuaded by SteadyMed's showing that an ordinarily skilled artisan, at the time of invention of the '393 patent, would have had reason to combine, and a reasonable expectation of success in combining, Moriarty and Phares. "[T]he

skilled artisan need not be motivated to combine [the prior art] for the same reason contemplated by [the inventor]." *In re Kahn*, 441 F.3d 977, 990 (Fed. Cir. 2006). In this regard, we note that in addition to teaching that intermediate purification is unnecessary to the production of treprostinil diethanolamine salt by the disclosed process (Ex. 1005, 40–42), Phares explicitly describes the Moriarty process in disclosing the production of (-)-treprostinil, the enantiomer of (+)-treprostinil (*id*. at 42). Ex. 1009 ¶¶ 50, 77–78. Accordingly, we are persuaded that an ordinarily skilled artisan would have modified the process of Moriarty to incorporate the step of adding and dissolving diethanolamine to treprostinil as taught by Phares (Ex. 1005, 24) to eliminate the requirement for intermediate purification, thus, improving synthetic efficiency and reducing cost.

UTC does not dispute either that the combination of Moriarty and Phares discloses treprostinil and treprostinil diethanolamine salt, or that the cited combination discloses steps (a)–(c) of claims 1 and 9. UTC contends, however, that an ordinarily skilled artisan would have had neither reason to combine, nor a reasonable expectation of success in combining Moriarty and Phares. PO Resp. 27–32. UTC additionally asserts that the salt formation recited in step (c) of the challenged claims yields unexpected improvements in both the overall purity and impurity profile of the treprostinil product. *Id*. UTC also argues that treprostinil diethanolamine salt produced according to the cited combination is physically different from treprostinil produced according to the '393 patent process. *Id*. at 28–30. Lastly, UTC asserts that evidence of objective indicia of nonobviousness,

including long-felt but unmet need and unexpected results, establish the nonobviousness of the challenged claims. *Id*. at 47–49. We address UTC's arguments below.

a. Level of Ordinary Skill in the Art

SteadyMed contends that a relevant skilled artisan would have had, at the time of invention of the '393 patent, "a master's degree or a Ph.D. in medicinal or organic chemistry, or a closely related field. (Ex. 1009, Winkler Decl., ¶ 14). Alternatively, a person of ordinary skill would include an individual with a bachelor's degree and at least five years of practical experience in medicinal or organic chemistry." Pet. 4.

UTC does not, in its Patent Owner Response, directly dispute SteadyMed's assertions with regard to the level of ordinary skill in the art, or argue that any differences in the skill levels advanced by the parties are relevant to the nonobviousness analysis. UTC's expert, Dr. Williams, however, advocates for a similar, albeit somewhat higher level of skill than is advanced by SteadyMed. In particular, Dr. Williams testifies that an ordinarily skilled artisan at the time of invention of the '393 patent would have had "a doctorate degree in chemistry, pharmaceutics, pharmaceutical sciences, medicine, or a related discipline. Alternatively, the POSA may have had a lesser degree in one of those fields, with correspondingly more experience." Ex. 2020 ¶ 33. Dr. Williams additionally testifies that "[t]o the extent necessary, a POSA may have collaborated with others of skill in the art, such that the individual and/or team collectively would have had experience in synthesizing and analyzing complex organic compounds." *Id*. Dr. Ruffolo, UTC's second expert,

agrees with Dr. Williams' opinions concerning the ordinarily level of skill in the art. Ex. 2022 ¶ 23.

We find that the level of ordinary skill in the art is reflected by the prior art of record. *See Okajima*, 261 F.3d at 1355. With respect to the slight variance in the educational attainment of a relevant artisan advanced by the parties, we agree with Drs. Williams and Ruffolo that an ordinarily skilled artisan at the time of invention of the '393 patent would have had a doctorate in chemistry, pharmaceutics, pharmaceutical sciences, medicine, or a related discipline, or a lesser degree in one of those fields, with correspondingly more experience. We also agree that the relevant skilled artisan may have collaborated with others of skill in the art, such that the individual and/or team collectively would have had experience in synthesizing and analyzing complex organic compounds. We observe, however, that our findings and legal conclusions apply with equal force whether the level of ordinary skill in the art advanced by SteadyMed or by UTC is adopted.

b. Rationale to Combine

UTC asserts that an ordinarily skilled artisan would not have had reason to combine Moriarty and Phares because Moriarty discloses the use of column chromatography for purification, and "Phares does not disclose any benefit or increased purity as a result of using the diethanolamine salt." PO Resp. 31. UTC additionally contends that Moriarty teaches three different ways to make treprostinil, and thus, an ordinarily skilled artisan would not have had reason to select the method that uses steps (a) and (b) recited in the challenged claims over the remaining two options. *Id*. at 27.

We do not agree. "[T]he problem motivating the patentee may be only one of many addressed by the patent's subject matter. . . . [A]ny need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *KSR*, 550 U.S. at 420; *see also Kahn*, 441 F.3d at 990 ("[T]he skilled artisan need not be motivated to combine [the prior art] for the same reason contemplated by [the inventor]."). Irrespective of whether Phares suggests any purity benefits over Moriarty, the proposed combination of Moriarty and Phares would eliminate the need for intermediate purification as required by Moriarty alone, and thereby confer efficiency and cost benefits. Ex. 1009 ¶¶ 77–78. We determine that an ordinarily skilled artisan would have sought to combine Moriarty and Phares in order to reap these efficiency and cost benefits.

We additionally find that an ordinarily skilled artisan would have sought to make the proposed combination for the independent reason that Phares is directed to improving treprostinil, and the Moriarty process, including the performance of steps (a) and (b) of the challenged claims, was a well-known way to make treprostinil. *See* Ex. 2059, 240:2–7, 244:10–21. "[I]f a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill." *KSR*, 550 U.S. at 417. For the same reason, we also find that an ordinarily skilled artisan would have had reason to combine the Moriarty process, including steps (a) and (b) of the challenged claims, with Phares. Indeed,

Phares itself describes the Moriarty process, including recited steps (a) and (b), with respect to producing the enantiomer of treprostinil. Ex. 1005, 42.

c. Reasonable Expectation of Success

Akin to its arguments concerning the rationale for combining Moriarty and Phares, UTC asserts that an ordinarily skilled artisan would not have had "a reasonable expectation of success by using salt formation as a purification step separate from or in addition to the column chromatography of Moriarty." PO Resp. 31. In particular, UTC contends that "Phares does not disclose any alleged benefit to forming the salt and a POSA would have no expectation that only certain acidic and neutral impurities would be reduced or completely eliminated while others remained." *Id*. at 31–32

But whether or not an ordinarily skilled artisan would have had an expectation that salt formation would improve the purity of Moriarty treprostinil is not the relevant inquiry. "The reasonable expectation of success requirement refers to the likelihood of success in combining references to meet the limitations of the claimed invention." *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016). It is undisputed that the proposed combination of Moriarty and Phares yields treprostinil diethanolamine salt, i.e., the product claimed in independent claims 1 and 9. Furthermore, as detailed in Part II.C.2.b above, both Moriarty treprostinil and Phares treprostinil diethanolamine salt are highly pure. Indeed, Phares treprostinil diethanolamine salt is at least as pure as that claimed in the '393 patent. Accordingly, we find that an ordinarily skilled artisan would have a

reasonable expectation of success in combining Moriarty and Phares.

d. A product comprising a compound [of/having] formula [I/IV] . . . or a pharmaceutically acceptable salt thereof

The present record supports SteadyMed's contention that the treprostinil diethanolamine salt disclosed by the combination of Moriarty and Phares is structurally identical to the pharmaceutically acceptable treprostinil diethanolamine salt recited in the challenged claims. Pet. 41–42; *see also* Ex. 1004, 6, 13; Ex. 1005, 24, 99 (claim 49); Ex. 1009 ¶ 76. As explained in Part II.C.2.a., above, it is undisputed that the treprostinil diethanolamine salt disclosed by Phares, which is the product that would result from the proposed combination, has the same chemical structure as the treprostinil diethanolamine salt claimed in the '393 patent.

e. Recited Process Steps

UTC does not dispute that the proposed combination of Moriarty and Phares discloses the process steps recited in the challenged product-by-process claims. Nevertheless, UTC contends that the claimed product is structurally different from prior art treprostinil products, and therefore, nonobvious. In addition to reiterating many of the arguments addressed in Part II.C.2.b., above, concerning the purported differences in the overall purity and impurity profile for treprostinil prepared according to the process described in the '393 patent versus that made according to prior art processes, UTC asserts that there is no basis for comparing the purity reported

in Moriarty to that reported in the Walsh Declaration submitted during prosecution of the '393 patent. PO Resp. 29. UTC also argues that Dr. Winkler's opinions concerning error in purity measurements are themselves erroneous, and should be disregarded.

First, we note that the absence of dispute concerning the disclosure of the recited process steps by the cited combination renders moot the question of whether the process steps recited in the challenged claims impart structural or functional differences to treprostinil so produced as compared to prior art treprostinil products. Because the combination of Moriarty and Phares discloses both the product claimed and the process recited in the challenged product-by-process claims, it renders those claims obvious.

Furthermore, as explained in Part II.C.2.b., above, we find that the evidence of record does not support the existence of any structural or functional differences between prior art treprostinil and that produced according to the '393 patent. Notably, our findings in this regard depend neither on comparison of the purity reported by Moriarty to that reported in the Walsh Declaration, nor on Dr. Winkler's opinions concerning error in purity measurements. Nevertheless, for completeness, we note that the 99.7% purity reported by Moriarty is the same as that derived from analysis of the purity of the commercial batch data for Moriarty treprostinil produced by UTC. We also observe, as explained in footnote 13, above, that the 99.7% HPLC purity assay value reported by Moriarty is reliable.

f. Claim 2

UTC asserts that the requirement for a product having a purity of at least 99.5% set forth in claim 2 is not rendered obvious by the combination of Phares and Moriarty because "there is no basis to compare the purity disclosed in Moriarty to the measurements obtained in the '393 patent or those obtained by Dr. Walsh in his declaration." PO Resp. 32.

We do not agree. The combination of Moriarty and Phares necessarily discloses treprostinil diethanolamine salt having a purity of at least 99.5%. First, as set forth above in Part II.C.2.c, Phares necessarily discloses treprostinil diethanolamine salt having a purity of 99.5% or higher. Second, as detailed in Part II.C.2.b., above, Moriarty treprostinil has an overall purity of 99.7%, thus, performing the purification disclosed by Phares on Moriarty would yield a product having at least as high a purity as the starting Moriarty treprostinil.

Furthermore, we find that the 99.7% purity reported in Moriarty is reliable and can be compared to the purity values reported in the '393 patent specification and Walsh Declaration. Moriarty discloses both that the purity of the disclosed treprostinil product was determined via an HPLC purity assay, and that Moriarty treprostinil "was identical in all respects to an authentic sample of UT-15 [treprostinil]". Ex. 1004, 13. The fact that Moriarty does not explicitly identify the reference standard used in the HPLC purity assay does not call into question the veracity of the purity reported. In this regard, we note that, like Moriarty, the '393 patent does not expressly identify the reference standard used for purity measurements.

See Paper 81, 18:1–3 ("The specification of the '393 patent does not identify the reference and neither does the Moriarty reference."). We also observe that reference standards are, just that—standards, and as such, the absence of information concerning the precise reference standard used does not call into question the validity of the purity reported in Moriarty.

g. Claims 8 and 16

Claims 8 and 16 depend from claims 1 and 9, respectively, and further recite "wherein the process does not include purifying the compound of formula [(III)/(IV)] produced in step (a)."

UTC contends that Moriarty teaches purification of the compound produced in step (a), and that Phares does not disclose treprostinil synthesis, or purification details. PO Resp. 32. On this basis, UTC concludes that the cited combination fails to render obvious claims 8 and 16. *Id*.

We do not agree. Rather, as explained in Part II.D.2.b., above, we find that the intermediate purification taught by Moriarty would be eliminated in the proposed combination with Phares. *See* Ex. 1009 ¶¶ 77–78. Accordingly, we agree with SteadyMed that an ordinarily skilled artisan in possession of Phares would have recognized that the alkylation step—step (a) of the challenged claims—"could be followed by the hydrolysis with a base without purifying the product of the alkylation reaction," and, further, would have recognized the elimination of the intermediate purification step from Moriarty as an advantage of combining Moriarty with Phares. Pet. 47–48; Ex. 1009 ¶¶ 77–78.

h. Objective Indicia of Nonobviousness

UTC contends that objective indicia of nonobviousness, including evidence of a long-felt but unmet need for treprostinil having greater overall purity and an improved impurity profile compared to treprostinil produced by known methods, as well as evidence that treprostinil produced according to the process steps of the challenged claims unexpectedly yields a product having increased purity as compared to prior art processes establishes that the challenged claims are nonobvious. PO Resp. 47–49.

Factual inquiries for an obviousness determination include secondary considerations based on evaluation and crediting of objective evidence of nonobviousness. *Graham*, 383 U.S. at 17. Notwithstanding what the teachings of the prior art would have suggested to a person of ordinary skill in the art at the time of the claimed invention, the totality of evidence submitted, including objective evidence of nonobviousness, may lead to a conclusion that the claimed invention would not have been obvious to one with ordinary skill in the art. *In re Piasecki*, 745 F.2d 1468, 1471–72 (Fed. Cir. 1984). Indeed, when present, evidence of objective indicia of nonobviousness, such as evidence of a long-felt but unmet need or unexpected results "may often be the most probative and cogent evidence [of nonobviousness] in the record." *Stratoflex*, 713 F.2d at 1538.

As explained below, however, upon full consideration of the evidence of record respecting the objective indicia of nonobviousness in this case, we are persuaded that nonobvious is not established by that evidence.

i. Long-Felt Need

Relying on the Ruffolo Declaration, UTC asserts that at the time of invention of the '393 patent, there existed a long-felt but unmet need for "a more efficient synthesis to produce treprostinil in a more pure form and in a cost-effective manner." PO Resp. 47. In this regard, UTC argues that because treprostinil is a potent drug, "any diastereomeric impurities would also potentially be potent." *Id*. at 48. UTC contends that "the FDA as a matter of course seeks to minimize all impurities in drug substances and particularly in highly potent drug substances such as treprostinil," and concludes that "[t]he reduction and removal of several types of impurities met the long-felt need expressed by the FDA to minimize impurities as much as possible." *Id*. UTC also asserts that its submission, and the FDA's adoption, of a change in UTC's drug specification for treprostinil increasing the purity from an assay range of 97.0%–101.0% to 98.0% to 102.0% for treprostinil produced according to the process disclosed in the '393 patent demonstrates satisfaction of the long-felt need, expressed by the FDA, for drug substances having fewer, and lower amounts of, impurities. *Id*. at 48–49.

In response, SteadyMed observes that UTC's expert, Dr. Ruffolo, does not offer any opinion concerning whether a long-felt need existed for higher purity versions of compounds other than treprostinil or treprostinil diethanolamine salt that fall within the scope of the challenged claims, and notes that claims 10, 14, 15, and 17 of the '393 patent are the only claims limited to treprostinil or its salt. Pet. Reply 23.

With regard to treprostinil and treprostinil diethanolamine salt, SteadyMed points out that Dr. Ruffolo conceded during deposition that he was unaware if the FDA had sought a change in purity, or if any party had expressed a particular desire for improved purity. *Id*. SteadyMed also notes that Dr. Ruffolo acknowledged that drug purity can typically be improved by repeating purification procedures, and that Dr. Williams testified that the purity of treprostinil could be improved using such an approach. *Id*. SteadyMed thus contends that there was no need for the claimed invention. *Id*. at 23–24. SteadyMed additionally asserts that Dr. Ruffolo acknowledged that the change in UTC's purity specification for Treprostinil accepted by the FDA was not a major amendment. *Id*. at 24.

SteadyMed further points out that treprostinil produced by prior art methods exceeds the 98% purity level required by the FDA, and that the FDA would permit the sale of treprostinil produced according to Moriarty. *Id*. SteadyMed also asserts that UTC has not identified any clinical difference between Moriarty treprostinil and treprostinil produced according to the method of the '393 patent. *Id*. Lastly, SteadyMed argues that Dr. Ruffolo's opinion should be disregarded because it relies on Dr. Williams' assertion that Moriarty treprostinil has an overall purity level of 99.0%. *Id*.

As an initial matter, we note that UTC's contentions regarding long-felt need are predicated on UTC's claim that treprostinil made according to the process described in the '393 patent has a higher purity, and different impurity profile than treprostinil produced by

other methods. However, as explained in Parts II.C.2.b. and II.D.2.e., above, the present record does not support that contention. We also observe that the purported differences between prior art treprostinil and the treprostinil claimed in the '393 patent derive solely from the process steps recited in the challenged product-by-process claims, and not the patented product itself. *See Purdue Pharma L.P. v. Epic Pharma, LLC*, 811 F.3d 1345, 1355 (Fed. Cir. 2016) (finding evidence of objective indicia of nonobviousness unpersuasive where such evidence relates to process steps recited in a product-by-process claim, rather than the "patented product").

Moreover, the evidence of record does not support a determination that a long-felt need existed for treprostinil having a higher overall purity, or improved purity profile than that exhibited by prior art treprostinil. "Absent a showing of long-felt need or the failure of others, the mere passage of time without the claimed invention is not evidence of nonobviousness." *Iron Grip Barbell Co., Inc. v. USA Sports, Inc.*, 392 F.3d 1317, 1325 (Fed. Cir. 2004).

UTC does not identify, and we do not discern evidence of record that any entity aside from UTC sought to produce treprostinil in a more pure form, via a more efficient synthesis, or in a more cost-effective manner than was possible using prior art processes. For example, even if we agree with UTC that because treprostinil is a "very potent drug so any diastereomeric impurities would also *potentially* be potent" (PO Resp. 48 (emphasis added)), the record is nevertheless devoid of evidence that any of those diastereomeric impurities are in fact potent, clinically

relevant, or otherwise of concern. *See e.g.*, Ex. 2022 ¶ 54 (noting that treprostinil "may contain trace amounts of potent structural analogs as impurities," but failing to identify what analogs are potent or to present evidence that such analogs are present in treprostinil produced according to prior art methods); Ex. 2058, 257:22–258:9, 315:15–23; Ex. 2059, 47:3–13.

Neither does the record include evidence to support UTC's assertion that "the FDA as a matter of course seeks to minimize all impurities in drug substances and particularly in highly potent drug substances such as treprostinil" (PO Resp. 48). UTC relies on Dr. Ruffolo's testimony in this regard, however, Dr. Ruffolo's opinion that "[a]s with all drug substances such as treprostinil, the FDA seeks to list, quantitate, and minimize impurities, and maximize the overall purity, of such drug substances as much as possible for the benefit of patients" (Ex. 2022 ¶ 31) is improperly conclusory. We give such testimony little or no weight. 37 C.F.R. § 42.65(a). Likewise, Dr. Ruffolo's opinion that "because some impurities are extremely toxic at very low levels of exposure, Thresholds of Toxicological Concern can, and often are, lowered, beyond the guidelines described above, in the specifications for the synthesis and manufacturing of a drug substance in order to be conservative" (Ex. 2022 ¶ 54), although supported by reference non-binding FDA industry guidance concerning mutagenic impurities, is insufficient to support the proposition that the FDA seeks, as a matter of course, to minimize all impurities in all pharmaceuticals, or in treprostinil in particular.

Moreover, even crediting UTC's contention that the FDA seeks to minimize all impurities in all

pharmaceuticals to the extent possible, such a general agency preference for improved purity is insufficient to establish a long-felt but unmet need for improved treprostinil, in particular. *See Tex. Instruments v. Int'l Trade Comm'n*, 988 F.2d 1165, 1178 (Fed. Cir. 1993) ("[L]ong-felt need is analyzed as of the date of an articulated identified problem and evidence of efforts to solve that problem."). Indeed, adherence to UTC's position would dictate a conclusion of nonobvious for any pharmaceutical product exhibiting any improvement in purity over prior art versions of that same product.

The record simply does not support a determination that the FDA sought a treprostinil product having an improved overall purity or different impurity profile versus known treprostinil products. UTC's reliance on its own request to the FDA for a change in the purity assay value for treprostinil as evidencing a long-felt need for improved treprostinil (PO Resp. 48) is misplaced. Far from indicating the existence of a long-felt need for improved treprostinil, the revised Drug Substance Specification (Ex. 2006) submitted by UTC to the FDA demonstrates only that the FDA had reservations concerning UTC's proposed change from manufacturing treprostinil by the Moriarty process to using the process described in the '393 patent. For example, the FDA notes its concerns that "[b]enzindene triol is not separated from the final intermediate (UT-I 5C intermediate) by several reaction steps *as is currently the case for the approved starting materials*" (Ex. 2006, 1 (emphasis added)) and that "[b]enzindene triol from several proposed suppliers *appears to result in carry over of impurities*" (*id*. at 2 (emphasis added)). The FDA also requests "a release specification for the

residual diethanolamine present in treprostinil (UT-15) manufactured . . . following the new manufacturing process." *Id*. at 7.

Furthermore, the FDA's ultimate approval of UTC's request for a change in the purity assay value for treprostinil from a range of 97%–101% to a range of 98%–102% does not evidence the existence of a long-felt need for improved treprostinil. First, it must be noted that the record indicates that UTC itself, not the FDA, sought the authorized change. Ex. 2006; *see also* Ex. 2058, 45:15–22. Second, as Dr. Ruffolo explains, "increasing the stringency of a—of a specification is not a major amendment" to that specification in and of itself. Ex. 2058, 310:5–13. Rather, "[w]hat is a major amendment was the change in the process, the change in the starting material." *Id*. at 310:13–18. Third, batches of Moriarty treprostinil satisfy the 98% minimum purity requirement for treprostinil approved by the FDA—regardless of whether those batches have an overall purity level of 99.7% as reported by Moriarty (Ex. 1004, 13), 99.05% as originally reported by Dr. Williams (Ex. 2020 ¶ 98), or 99.7% as obtained when development batches are excluded from Dr. Williams' analysis (Ex. 1021; Ex. 2059, 218:3–20)—and could be sold to the public (Ex. 2058, 179:23–180:17). Fourth, UTC does not identify, and we do not discern evidence to support the existence of any clinical or safety differences between Moriarty treprostinil, and treprostinil produced according to the '393 patent. *See, e.g.*, Ex. 2058, 257:22–258:9, 315:15–23; Ex. 2059, 47:3–13.

Lastly, we observe that to the extent UTC argues that a long-felt need existed not merely for treprostinil

having an improved purity, but for "a more efficient synthesis to produce treprostinil in a more pure form and in a cost-effective manner" (PO Resp. 47), or for "a commercial scale synthesis of treprostinil that results in a treprostinil product with higher overall purity and lower levels of individual impurities" (Ex. 2022 ¶ 31), the challenged claims are not directed to an efficient, cost-effective, or commercial scale synthesis, and thus, cannot be said to satisfy such a need.

Alternatively, we determine that even if UTC had shown that the challenged claims satisfied a long-felt need for treprostinil having a purportedly improved purity, this secondary consideration does not undermine SteadyMed's proof of obviousness in this case. Although secondary considerations must be taken into account, they do not necessarily control the obviousness conclusion. *Newell Cos., Inc. v. Kenney Mfg. Co.*, 864 F.2d 757, 768 (Fed. Cir. 1988). Here, the record establishes such a strong case of obviousness that UTC's allegedly unexpectedly superior results would nevertheless be insufficient to establish nonobviousness. *Id*. at 769.

Accordingly, for the reasons set forth above, we find that the present record does not support a determination that the product of the challenged claims satisfied a long-felt but unmet need.

ii. Unexpected Results

UTC contends that "[t]he use of a salt form of treprostinil to further purify the treprostinil acid in a cheaper and better way than the previously used methods of purification was an unexpected result." PO Resp. 49. Relying on the Williams Declaration, UTC

asserts that the salt purification step recited in the challenged claims unexpectedly reduced both diastereomeric impurities and certain non-acidic impurities. *Id*. In particular, UTC argues that Eğe predicted only the removal of basic and neutral impurities when an acid is used in salt purification, and contends that the reduction of some, but not all non-acidic impurities highlights the unpredictability of the observed results. *Id*.

As an initial matter, we note that UTC's contentions regarding unexpected results are predicated on UTC's claim that treprostinil made according to the process described in the '393 patent has fewer impurities than treprostinil produced by other methods. However, as explained in Parts II.C.2.b., II.D.2.e., and II.E.3.d., the present record does not support that contention. *See In re Geisler*, 116 F.3d 1465, 1470 (Fed. Cir. 1997) ("[I]t is well settled that unexpected results must be established by factual evidence."); *cf.*, *Epic Pharma*, 811 F.3d at 1355 (finding evidence of objective indicia of nonobviousness unpersuasive where such evidence relates to process steps recited in a product-by-process claim, rather than the "patented product" itself).

Furthermore, we observe that UTC does not offer evidence to support the contention that "[t]he use of a salt form of treprostinil to further purify the treprostinil acid in a cheaper and better way than the previously used methods of purification was an unexpected result." In particular, we note that UTC does not identify evidence of record to support a determination that salt purification and free acid regeneration is a "better" way to produce treprostinil. Neither does UTC identify evidence to demonstrate the

cost savings associated with salt formation purification, much less establish that cost savings as unexpected. *See In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995) (explaining that unexpected results are useful to show the "improved properties provided by the claimed compositions are much greater than would have been predicted" (internal quotation omitted)).

With regard to the purportedly unexpected result that salt purification reduced some, but not all acidic impurities, including certain stereoisomers, as well as certain non-acidic impurities, we find that these results are not unexpected. For example, Kawakami, discussed in detail in Part II.E., below, expressly describes the use of salt purification to improve the purity of a methanoprostacyclin derivative (Ex. 1007, 6), which like treprostinil, is a prostacyclin compound. Notably, Kawakami teaches the reduction of stereoisomers, in addition to other impurities, through salt formation and subsequent free acid regeneration, suggesting, contrary to UTC's position, that the purported reduction in acidic stereoisomeric impurities obtained via the process steps recited in the challenged claims was not unexpected.

Finally, even crediting UTC's contention that salt purification unpredictably reduced some, but not other impurities, without more, such evidence would nevertheless be insufficient to establish unexpected results. *See Soni*, 54 F.3d at 751 ("Mere improvement in properties does not always suffice to show unexpected results."). In this regard, we observe that the miniscule amounts of impurities present in both prior art and '393 patent treprostinil, combined with the significant inter-batch variation in impurity types

and amounts between batches of treprostinil render the impurity differences alleged by UTC not unexpected. *See In re Eli Lilly & Co.*, 902 F.2d 943, 948 (Fed. Cir. 1990) (requiring a showing that "a significant aspect of [the] claimed invention is unexpected in light of the prior art" to establish nonobviousness).

Alternatively, we determine that even if UTC had shown that the challenged claims produce unexpectedly superior treprostinil, this secondary consideration does not overcome the strong showing of obviousness in this case. Although secondary considerations must be taken into account, they do not necessarily control the obviousness conclusion. *Newell Cos.*, 864 F.2d at 768. Here, the record establishes such a strong case of obviousness that UTC's allegedly unexpectedly superior results would nevertheless be insufficient to establish nonobviousness. *Id*. at 769.

Accordingly, for the reasons set forth above, we find that the present record does not support a determination that the product of the challenged claims was unexpectedly superior to the prior art.

iii. Process Advantages

With respect to claims 8 and 16, UTC states, without further explanation that "[p]rocess advantages should be considered as secondary considerations to rebut obviousness, even if the process steps or advantages are not considered" in comparing the challenged claims to the prior art. PO Resp. 32.

Although we agree that all evidence of objective indicia must be considered in evaluating obviousness, we observe that UTC does not identify what evidence of "process advantages" should be taken into account,

or how it should be evaluated. Accordingly, we determine that the present record does not support a determination that the challenged claims presented process advantages sufficient to overcome the strong showing of obviousness.

For the foregoing reasons, therefore, based on the entire record before us, we find that the evidence of objective indicia of nonobviousness does not undermine SteadyMed's proof of obviousness in this case. Alternatively, we determine that even if UTC had shown that the challenged claims satisfied a long-felt need for treprostinil of allegedly greater purity, produced unexpectedly superior treprostinil, and afforded process advantages as claimed, this evidence would not undermine SteadyMed's proof of obviousness.

3. Conclusion

UTC does not separately argue claims 3–5, 7, 8, 11–14, and 16–20. *See* PO Resp. 27–33. We have reviewed Petitioner's evidence and argument as to those claims, and conclude that Petitioner has established by a preponderance of the evidence that Moriarty and Phares would have rendered obvious to one with ordinary skill in the art the subject matter recited in those claims. Pet. 45–48, 50–52.

For the foregoing reasons, therefore, we determine SteadyMed has demonstrated, by a preponderance of the evidence, that the combination of Moriarty and Phares would have rendered obvious to one with ordinary skill in the art the subject matter recited in claims 1–5, 7–9, 11–14, and 16–20.

E. Obviousness Grounds of Unpatentability Based on Moriarty, Phares, Kawakami, and Eğe

SteadyMed asserts that claims 6, 10, 15, 21, and 22 are unpatentable under § 103(a) as obvious in view of Moriarty, Phares or Kawakami, and Eğe. Pet. 37–52. As explained in the Decision on Institution (Dec. 37), although SteadyMed nominally identifies this ground of unpatentability as being over "Moriarty (Ex. 1004) with Phares (Ex. 1005) or Kawakami (Exs. 1006 & 1007) and in further combination with Ege (Ex. 1008)" (Pet. 53 (emphasis omitted)), SteadyMed explicitly relies on Kawakami in arguing unpatentability in view of Moriarty, Phares, and Eğe. Accordingly, as set forth in the Decision on Institution, we understand SteadyMed's stated ground of unpatentability as relying on the combination of Moriarty, Phares, Kawakami, and Eğe. Dec. 37.

Claims 6, 21, and 22 depend, directly or indirectly, from claim 1, and claims 10 and 15 depend directly from claim 9. In support of its assertion, SteadyMed provides detailed explanations as to how the combination of Moriarty, Eğe, Phares, and Kawakami discloses each claim limitation (*id.*), and relies upon the Winkler Declaration (Ex. 1009) and the Rogers Declaration (Ex. 1022) to support its positions.

1. Kawakami

Kawakami describes "a crystalline dicyclohexylamine salt of a methanoprostacyclin derivative, a manufacturing method thereof, and a purifying method thereof." Ex. 1007, 3. Kawakami discloses obtaining a dicyclohexylamine salt by "mixing a methanoprostacyclin derivative [I] . . . with

dicyclohexylamine in an appropriate solvent." Ex. 1007, 5–6. Kawakami explains that "[t]he dicyclohexylamine salt of the methanoprostacyclin derivative [I] thus obtained generally has fairly high purity, and the purity can be further improved by recrystallization as needed with the use of an appropriate solvent." *Id*. at 6.

Kawakami further teaches that "[t]he dicyclohexylamine salt obtained by the present invention can be easily reverted to a free methanoprostacyclin derivative [I] by conventional methods, and the resulting methanoprostacyclin derivative exhibits excellent crystallinity compared with substances not purified according to the present invention." *Id*.

2. Eğe

Eğe is an organic chemistry textbook. Ex. 1008, 1. Eğe discloses:

> Carboxylic acids that have low solubility in water, such as benzoic acid, are converted to water-soluble salts by reaction with aqueous base. Protonation of the carboxylate anion by a strong acid regenerates the water-insoluble acid. These properties of carboxylic acids are useful in separating them from reaction mixtures containing neutral and basic compounds.

Id. at 8 (reference omitted).

3. Discussion

Claims 6, 10, 15, 21, and 22 each recite the product of either claim 1 or claim 9, subject to additional

process steps. Notably, each of claims 6, 10, 15, 21, and 22 requires the performance of step (d) recited in claims 1 and 9, but identified as optional in the independent claims.

SteadyMed contends that the combination of Moriarty, Phares, Kawakami, and Eğe discloses the treprostinil products recited in claims 6, 10, 15, 21, and 22 of the '393 patent. Pet. 53–57. SteadyMed also asserts that the combination of Moriarty, Phares, Kawakami, and Eğe discloses steps (a)–(d) required by the challenged claims. *Id*.

We have reviewed the Petition and the supporting evidence to which we are directed as to how the combination of Moriarty, Phares, Kawakami, and Eğe discloses each limitation of the challenged claims. We are persuaded by SteadyMed's showing that the combination of Moriarty, Phares, Kawakami, and Eğe discloses both the treprostinil products claimed, as well as the production of treprostinil diethanolamine salt through the performance of steps (a)–(d) recited in the challenged claims of the '393 patent.

Relying on its expert, Dr. Winkler, SteadyMed asserts that a relevant skilled artisan would add further purification steps as taught by Kawakami and Eğe to the combination of Moriarty and Phares described in Part II.D.2., above, to further improve the treprostinil product. Pet. 53–54. In this regard, SteadyMed contends that Kawakami discloses prostacyclin compounds, of which treprostinil is one example, can be purified by using weak bases and forming salts, which can then be converted back into free acid form. Pet. 43. In particular, SteadyMed argues that Kawakami "discloses that the

dicyclohexylamine salt of a methanoprostacyclin derivative 'can be easily reverted to the free methanoprostacyclin derivative by *conventional methods*,'" and that the "fairly high purity" of the salt obtained "can be further improved by recrystallization as needed with the use of an appropriate solvent." Pet. 53.

In addition, Dr. Winkler testifies that, as evidenced by Eğe, a relevant skilled artisan "would understand that one such conventional method for converting the dicyclohexylamine salt of a methanoprostacyclin derivative to the free methanoprostacyclin derivative, or converting the treprostinil diethanolamine salt to treprostinil (*i.e.*, the free acid) is by treating the salt with a strong acid such as HCl or H_2SO_4." Ex. 1009 ¶ 84; *see also* Pet. 53–54. Dr. Winkler elaborates on this rationale for combining the cited references, testifying that a relevant skilled artisan would

> want to form the treprostinil diethanolamine salt, purify it, and then convert it back to its free form (*i.e.*, treprostinil) in order to obtain excellent crystallinity and increased purity. And Ege (Ex. 1008, p. 8) teaches that one such method for obtaining the free form of treprostinil or any carboxylic acid would be by treatment of the carboxylate salt with a strong acid.

Ex. 1009 ¶ 88; *see also* Ex. 1008, 8; Pet. 54.

Notwithstanding UTC's arguments to the contrary, which we address below, we are persuaded by SteadyMed's showing that an ordinarily skilled artisan, at the time of invention of the '393 patent, would have had reason to combine, and a reasonable expectation of

success in combining, Moriarty, Phares, Kawakami, and Eğe. "[I]f a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill." *KSR*, 550 U.S. at 417. We are persuaded that an ordinarily skilled artisan would have modified the above-described combination of Moriarty and Phares to further include carboxylate salt formation and neutral carboxylic acid regeneration steps, as taught by Kawakami, because Kawakami discloses that this purification and free acid regeneration procedure results in excellent crystallinity and improved purity for prostacyclin compounds. Ex. 1007, 6. We are additionally persuaded that a relevant skilled artisan would have sought to use a strong acid to regenerate treprostinil free acid, because Kawakami discloses the use of "conventional methods" to regenerate prostacyclin free acids (*id.*), and Eğe teaches that treatment of a carboxylate salt, such as treprostinil, with a strong acid will yield a free form of the carboxylic acid. Ex. 1008, 8.

UTC does not dispute either that the combination of Moriarty, Phares, Kawakami, and Eğe discloses treprostinil and treprostinil diethanolamine salt, or that the cited combination discloses steps (a)–(d) of independent claims 1 and 9, as required by the challenged claims. Akin to its arguments above concerning anticipation by Phares and obviousness in view of Moriarty and Phares, UTC asserts that the treprostinil products of the challenged claims are structurally and functionally different than those described in the prior art. PO Resp. 33–34. UTC also

contends that any "close" structural similarity between Moriarty treprostinil and the claimed invention is insufficient to support a conclusion of obviousness. *Id*. at 45. In addition, UTC argues that an ordinarily skilled artisan would not have had reason to, or a reasonable expectation of success in combining Kawakami and Eğe with Moriarty and Phares. *Id*. at 34–44. UTC further asserts that the cited combination fails to disclose certain process steps and purity requirements recited in the challenged claims. *Id*. at 45–47. Lastly, UTC contends that evidence of objective indicia of nonobviousness, including long-felt but unmet need and unexpected results, establish the nonobviousness of the challenged claims. *Id*. at 47–49. We address UTC's arguments below.

a. Level of Ordinary Skill in the Art

For the reasons set forth above, we apply in our analysis of the obviousness of the challenged claims in view of Moriarty, Phares, Kawakami, and Eğe the same level of ordinarily skill in the art at the time of invention of the '393 patent as described in Part II.D.2.a.

b. Rationale to Combine

UTC asserts that because the level of skill in the chemical arts in general, and in relation to the claimed invention in particular, is high, an ordinarily skilled artisan would not have looked to an undergraduate textbook such as Eğe to identify improved purification techniques for a complex drug such as treprostinil. PO Resp. 35–36. UTC argues also that neither Phares nor Eğe provides reason for a relevant skilled artisan to include a carboxylate salt formation and neutral acid

regeneration step in treprostinil synthesis. *Id*. at 37. In this regard, UTC states that there is no suggestion in Phares to convert treprostinil diethanolamine salt back to the free acid (*id*.), and asserts that Eğe teaches away from the use of salt formation and free acid regeneration to remove acidic compounds, such as certain acidic stereoisomers found in treprostinil (*id*. at 38). On this basis, UTC concludes that a relevant skilled artisan "would have understood Moriarty, Phares, and Eğe to suggest simply making the treprostinil free acid product of Moriarty, and not undergoing the additional time and expense of a 'carboxylate salt formation and regeneration of the neutral carboxylic acid' step." *Id*.

UTC additionally argues that Kawakami's teachings would not have provided reason to add a carboxylate salt formation and neutral acid regeneration step to the method for treprostinil synthesis disclosed by Moriarty and Phares because the prostacyclins described in Kawakami are "structurally very different" from treprostinil, and thus, the purification of treprostinil is quite different from the prostacyclin purification described by Kawakami. *Id*. at 39–41. UTC further asserts that Kawakami teaches away from the salts recited in claims 14 and 18 of the '393 patent. UTC thus concludes that an ordinarily skilled artisan would not have looked to Kawakami or Eğe to improve treprostinil purification, because neither reference discloses how to remove stereoisomeric impurities. *Id*. at 41.

We do not find UTC's arguments persuasive. As explained above, we find that a relevant skilled artisan would have had reason to add a carboxylate salt

formation and neutral acid regeneration step to the method of Moriarty and Phares described above based on Kawakami's teachings that prostacyclin compounds can be purified by using weak bases and forming salts that can subsequently be converted back into free acids of improved purity and crystallinity by conventional methods, and Eğe's teachings that strong acids are useful in such a conversion. Accordingly, it is of no moment whether Phares itself suggests the conversion of treprostinil diethanolamine salt back into free acid form. It is likewise irrelevant that Eğe is an introductory text. Kawakami encourages the use of "conventional methods" to regenerate the free acid. Ex. 1007, 6. As a basic chemistry text, there can be no dispute that Eğe teaches precisely that—namely, a conventional method for regenerating a free acid using a strong acid. Furthermore, the fact that Eğe is an introductory text does not demean its value as prior art.

Neither do we find persuasive UTC' assertion that Eğe teaches away from the claimed invention because it discloses that salt formation and free acid regeneration is only useful to remove neutral and basic impurities, not acidic impurities, such as certain acidic stereoisomers present in treprostinil. As an initial matter, we observe that the '393 patent, as well as the prior art of record, is silent as to the specific impurities present in treprostinil, as well as whether those impurities are acidic. Accordingly, we agree with SteadyMed (Pet. Reply 19) that undisclosed information about the impurities present in treprostinil cannot defeat the rationale for using crystallization discussed above. This is particularly true where, as here, the record indicates that Kawakami teaches the

use of crystallization to separate stereoisomers. Ex. 2051, 203:4–204:20.

Moreover, even crediting UTC's position we observe that Eğe's teachings concerning the removal of neutral and basic impurities nevertheless support the proposed combination because the procedure disclosed would be effective for removing neutral and basic impurities, regardless of the impact on acidic impurities (Pet. 53–55; Ex. 1009 ¶¶ 86, 88). *See In re Kahn*, 441 F.3d at 988 ("[T]he skilled artisan need not be motivated to combine [the prior art] for the same reason contemplated by [the inventor]."). Indeed, as explained above, the evidence of record indicates that treprostinil diethanolamine salt formation followed by regeneration of treprostinil using a strong acid is an effective purification step. Pet. 53–55; *see also* Ex. 1007, 6; Ex. 1008, 8; Ex. 1009 ¶¶ 82–90. Accordingly, contrary to UTC's intimations, this is not a case where "there would have been no reason to incur additional time and expense to form a salt of the valuable, relatively pure Moriarty treprostinil free acid only to then convert it back to the free acid, even though the addition would have been technologically possible." PO Resp. 44. Rather, an ordinarily skilled artisan would have expected that salt formation and free acid regeneration would yield a highly pure, crystalline product.

With regard to the level of similarity between treprostinil and the methanoprostacyclin derivative described by Kawakami, we disagree with UTC's contention that these compounds are dissimilar, and that an ordinarily skilled artisan thus would not have turned to Kawakami for guidance regarding the purification of treprostinil. In this regard, we note that

both Kawakami's methanoprostacyclin derivative and treprostinil are prostacyclins. We also observe that their chemical structures are similar. Ex. 1028. In addition, we do not agree with UTC's assessment that Kawakami's methanoprostacyclin derivative and treprostinil are not improved in the same way by salt formation and free acid regeneration. To the contrary, both compounds exhibit higher overall purity, as well as a reduction in stereoisomer impurities subsequent to treatment.

Turning to UTC's contentions regarding differences between the salt used in Kawakami and the salts recited in claims 14 and 18, we observe that those claims are not challenged under this ground of unpatentability. We further note that Kawakami's teachings do not affect our determination, set forth above, that claims 14 and 18 are anticipated by Phares and obvious in view of Moriarty and Phares.

Accordingly, on the record before us, we find that SteadyMed has sufficiently demonstrated that one of ordinary skill in the art would have included the carboxylate salt formation and regeneration of the neutral carboxylic acid of Eğe with the syntheses of Moriarty and Phares based on Kawakami's disclosure that the conversion of salts of prostacyclin derivatives to their free forms by conventional methods increases purity and crystallinity of the final product. *See KSR*, 550 U.S. at 417.

c. Reasonable Expectation of Success

UTC recasts several of the same arguments addressed above with respect to the rationale to combine the cited references as supporting a

determination that an ordinarily skilled artisan would not have had a reasonable expectation of success in the proposed combination of Moriarty, Phares, Kawakami, and Eğe. PO Resp. 37, 42–44. In particular, UTC asserts that a relevant skilled artisan would not have had a reasonable expectation of success in further purifying the treprostinil product of Moriarty using carboxylate salt formation and neutral carboxylic acid regeneration. *Id*. at 37. UTC also argues that treprostinil purification is "quite different" from the purification of the methanoprostacyclin derivative described by Kawakami, and, thus, an ordinarily skilled artisan would have had no reasonable expectation of success in applying the methods of Kawakami to purify treprostinil. *Id*. at 42.

We do not agree. As explained in Part II.D.2.c., above, whether or not an ordinarily skilled artisan would have had an expectation that salt formation and free acid regeneration would improve the purity of Moriarty treprostinil is not the relevant inquiry. *See Intelligent Bio-Sys.*, 821 F.3d at 1367 ("The reasonable expectation of success requirement refers to the likelihood of success in combining references to meet the limitations of the claimed invention."). It is undisputed that the proposed combination yields treprostinil. Furthermore, as detailed in Parts II.C.2.b. and II.D.2.e., above, both Moriarty treprostinil and Phares treprostinil diethanolamine salt are highly pure, and Kawakami shows that salt formation and free acid regeneration is an effective technique for purifying a prostacyclin compound (Ex. 1007, 6).

In addition, for the same reasons set forth with respect to the rationale to combine Moriarty, Phares,

Kawakami, and Eğe, we find that Kawakami's methanoprostacyclin derivative and treprostinil are sufficiently similar that an ordinarily skilled artisan would have had a reasonable expectation of success in using the salt formation and free acid regeneration prostacyclin purification procedure taught by Kawakami to purify treprostinil. In this regard, we recognize, but do not find persuasive, UTC's contention that differences in the particular stereoisomers and other impurities removed from treprostinil and Kawakami's methanoprostacyclin derivative using salt formation and free acid regeneration would have foreclosed any reasonable expectation of success. *See In re Longi*, 759 F.2d 887, 897 (Fed. Cir. 1985) ("Only a reasonable expectation of success, not absolute predictability, is necessary for a conclusion of obviousness.").

Accordingly, we find that an ordinarily skilled artisan would have a reasonable expectation of success in combining Moriarty, Phares, Kawakami, and Eğe to produce treprostinil.

d. Recited Process Steps

UTC reasserts its contention, addressed in Parts II.C.2.b. and II.D.2.e., above, that the treprostinil products of the challenged claims exhibit structural and functional differences compared to prior art treprostinil. PO Resp. 33–34. In particular, UTC argues that the performance of step (d) as required by claims 6, 10, 15, 21, and 22 imparts a higher overall purity, as well as an improved purity profile relative to the treprostinil produced by Moriarty. *Id*. at 33. UTC also asserts that "Phares' diethanolamine salt of treprostinil is structurally and functionally distinct from the free

acid substance formed by step (d) of claims 6, 15 and 21." *Id*. UTC relies on the same evidence and reasoning addressed previously in making these arguments. In addition, UTC contends that even if a "close relationship" exists between Moriarty treprostinil and the treprostinil of the challenged claims, "conducting a salt-formation purification step on the known treprostinil free acid of Moriarty would not have been obvious, so the mere existence of a 'close relationship' in the products cannot be used to deny patentability." *Id*. at 45.

As explained in Parts II.C.2.b. and II.D.2.e., above, we find that the evidence of record does not support the existence of any structural or functional differences between prior art treprostinil and that produced according to the '393 patent. Furthermore, we observe that UTC's argument concerning the effect of a "close relationship" between Moriarty treprostinil and that of the challenged claims is a non-sequitur. As explained previously, we find that no structural or functional differences exist between Moriarty treprostinil and '393 patent treprostinil, and, therefore, conclude that the process steps recited in the '393 patent are not entitled to patentable weight. Moreover, even were the recited process steps entitled to patentable weight, as explained-in-part above, and addressed further below, we nevertheless determine that the recited process steps would have been obvious to a relevant skilled artisan.

e. Claims 6, 15, and 21

Claims 6, 15, and 21 each recite the product of either claim 1 or claim 9, subject to additional process steps. Claim 6 recites "[t]he product of claim 1, wherein

the acid in step (d) is HCl or H_2SO_4." Claim 15 similarly recites "[t]he product of claim 9, wherein the acid in step (d) is HCl." Claim 21 simply recites "[t]he product of claim 1, wherein step (d) is performed."

UTC does not offer evidence or argument to suggest that the additional process steps recited in claims 6, 15, and 21 impart structural or functional differences to the claimed product beyond that discussed above in Parts II.C.2.b, II.D.2.e, and II.E.3.d. Rather, UTC reiterates the argument, addressed above, that a relevant skilled artisan "would not have looked to Eğe to further purify a complex carboxylic acid such as treprostinil from its stereoisomers and other impurities and would have no reasonable expectation of success by using HCl based on this disclosure." PO Resp. 46 (quoting Ex. 2020 ¶ 115).

It is undisputed that Eğe discloses the conversion of the carboxylate salt sodium benzoate back to the carboxylic acid benzoic acid by treatment with the acid HCl. Ex. 1008, 8; *see* PO Resp. 46 ("Eğe cites HCl as an example in the conversion of benzoic acid"). Moreover, as detailed in Parts II.E.3.b.–c. above, we find that an ordinarily skilled artisan at the time of invention of the '393 patent would have had reason to, and a reasonable expectation of success in, combining Moriarty, Phares, Kawakami, and Eğe. Accordingly, we do not find UTC's position persuasive.

f. Claim 10

Claim 10 recites "[t]he product of claim 9, wherein the purity of product of step (d) is at least 99.5%." Ex. 1001, 20:47–48.

UTC advances the same argument addressed above, in Part II.D.2.f., concerning claim 2, concerning the comparability of the 99.7% purity reported by Moriarty and that recited in claim 10. PO Resp. 46. In addition, UTC reasserts its contentions, addressed above, in Parts II.E.3.b.–c., that Moriarty does not perform steps (c) or (d) of the challenged claims, and that a relevant skilled artisan would not have had reason to, or a reasonable expectation of success in, looking to Phares, Kawakami, or Eğe to improve the purity of treprostinil. *Id*.

For the same reasons set forth with regard to claim 2, we find that the 99.7% purity reported by Moriarty is reliable, and thus, performing the additional purification steps disclosed by Phares, Kawakami, and Eğe on Moriarty would yield a product having at least as high a purity as the starting Moriarty treprostinil. Furthermore, as explained above, we find that an ordinarily skilled artisan would have had reason to, and a reasonable expectation of success in, combining Moriarty, Phares, Kawakami, and Eğe, in order to produce a treprostinil product of greater purity.

g. Claim 22

Claim 22 recites "[t]he product of claim 21, wherein the product comprises a pharmaceutically acceptable salt formed from the product of step (d)."

UTC asserts that the cited combination fails to disclose the additional salt formation step recited in claim 22, but does not offer evidence or argument to suggest that this process step imparts structural or functional differences to the claimed product beyond

that discussed above in Parts II.C.2.b., II.D.2.e., and II.E.3.d.

It is undisputed that the cited combination discloses treprostinil diethanolamine salt. Moreover, as explained previously, we find that the evidence of record does not support the existence of any structural or functional differences between prior art treprostinil diethanolamine salt and that produced according to the '393 patent.

h. Objective Indicia of Nonobviousness

UTC reasserts its position, addressed in Part II.D.2.h., above, that objective indicia of nonobviousness, including evidence of a long-felt but unmet need for treprostinil having greater overall purity and an improved impurity profile compared to treprostinil produced by known methods, as well as evidence that treprostinil produced according to the process steps of the challenged claims unexpectedly yields a product having increased purity as compared to prior art processes establish the nonobviousness of the challenged claims. PO Resp. 47–49.

As explained in detail above, however, upon full consideration of the evidence of record respecting the objective indicia of nonobviousness in this case, we are persuaded that nonobvious is not established by that evidence.

4. Conclusion

For the foregoing reasons, therefore, we determine SteadyMed has demonstrated, by a preponderance of the evidence, that the combination of Moriarty, Phares, Kawakami, and Eğe would have rendered obvious to

one with ordinary skill in the art the subject matter recited in claims 6, 10, 15, 21, and 22.

F. SteadyMed's Motion to Exclude Evidence

SteadyMed moves to exclude the Ruffolo Declaration (Ex. 2022), concerning the existence of a long-felt but unmet need for the claimed invention because, according to SteadyMed, Dr. Ruffolo applied an incorrect legal standard in rendering his opinions. Paper 63, 1. SteadyMed contends that Dr. Ruffolo's opinions are "unreliable, confusing, and not helpful to the trier of fact." *Id*.

Even without excluding the Ruffolo Declaration, however, we have determined that SteadyMed has demonstrated, by a preponderance of the evidence, that claims 1–22 of the '393 patent are unpatentable.

Accordingly, SteadyMed's Motion to Exclude is *dismissed* as moot.

G. UTC's Motion to Exclude Evidence

UTC seeks to exclude the following: (1) certain portions of the Winkler Declaration (Ex. 1009); (2) a website printout entitled "Getting Started in HPLC,' Section 4D: Precision and Accuracy" (Ex. 1017); (3) certain portions of the Rogers Declaration (Ex. 1022); and (4) certain portions of the Deposition Transcript of Dr. Robert M. Williams, Ph.D. (Ex. 2059). Paper 65, 2. UTC additionally seeks to exclude the portions of the Petition and Petitioner's Reply to Patent Owner's Response that rely on these exhibits. *Id*. at 3.

1. Winkler Declaration (Ex. 1009)

UTC contends that paragraphs 3, 31, 46, 48, 54, 57, 63, 71, and 72 of the Winkler Declaration (Ex. 1009) should be excluded because the testimony in these paragraphs represent "purely legal conclusions or otherwise unsupported conclusory statements." PO Mot. Exclude 6.

SteadyMed responds that the testimony objected to merely summarizes Dr. Winkler's ultimate conclusions on issues of anticipation and obviousness, and is therefore admissible. Pet. Opp. Exclude 2.

We are not persuaded by UTC's arguments. It is blackletter law that "[a]n opinion is not objectionable just because it embraces an ultimate issue." Fed. R. Evid. 704(a). Furthermore, it is within our discretion to assign the appropriate weight to be accorded to evidence. In its motion, UTC has not explained adequately why we should exclude conclusory expert testimony, instead of giving it little or no weight. *See, e.g.*, *Donnelly Garment Co. v. NLRB*, 123 F.2d 215, 224 (8th Cir. 1941) ("One who is capable of ruling accurately upon the admissibility of evidence is equally capable of sifting it accurately after it has been received . . . .").

For the foregoing reasons, we decline to exclude any portion of the Winkler Declaration (Ex. 1009).

2. Website Printout: "Getting Started in HPLC,' Section 4D: Precision and Accuracy" (Ex. 1017)

UTC contends that Exhibit 1017, a website printout entitled "Getting Started in HPLC,' Section 4D: Precision and Accuracy," should be excluded as

inadmissible hearsay. PO Mot. Exclude 7. UTC additionally asserts that Exhibit 1017 has not been authenticated, and should be excluded on that basis as well. UTC contends that Ex. 1017 itself, as well as paragraph 70 of the Winkler Declaration, and the portions of the Petition and Petitioner's Reply to Patent Owner's Response that rely on Exhibit 1017 or paragraph 70 of the Winkler Declaration should be excluded.

SteadyMed responds that Dr. Winkler's reliance on Exhibit 1017 to support his assessment of error in HPLC instrumentation was proper, irrespective of the Exhibit's status as hearsay. Pet. Opp. Exclude 5. SteadyMed argues also that Exhibit 1017 is not hearsay and is properly authenticated. *Id*. at 6.

As an initial matter, we determine that Dr. Winkler is entitled to rely on Exhibit 1017 as support for his opinions. Fed. R. Evid. 703. While we recognize UTC's contention that an expert in pharmaceutical purity would not rely on a general HPLC printout to determine instrumentation error rates (PO Reply Exclude 2), we do not find UTC's position persuasive. In this regard, we observe that Dr. Winkler relies on Exhibit 1017 solely as providing a baseline understanding of the relative standard deviation for HPLC instrumentation. Ex. 1009 ¶ 70. We also observe that it is within our discretion to assign the appropriate weight to be accorded to evidence, and UTC has not explained adequately why we should exclude Dr. Winkler's testimony, instead of giving it little or no weight. *See, e.g.*, *Donnelly Garment Co.*, 123 F.2d at 224.

As to the portions of the Petition and Petitioner's Reply to Patent Owner's Response that UTC seeks to exclude as improperly relying on paragraph 70 of the Winkler Declaration or Exhibit 1017, we note that SteadyMed's pleadings rely exclusively on Dr. Winkler's opinions as set forth in paragraph 70 of his declaration, and not on Exhibit 1017 itself. Accordingly, because we determine that Dr. Winkler's opinions are admissible, we decline to exclude the portions of the Petition and Petitioner's Reply to Patent Owner's Response identified by UTC.

With respect to Exhibit 1017 itself, we do not rely on that Exhibit in our decision, and, therefore, determine that as it pertains to Exhibit 1017, UTC's motion to exclude is moot.

For the foregoing reasons, we decline to exclude paragraph 70 of the Winkler Declaration (Ex. 1009), as well as the portions of the Petition and Petitioner's Reply to Patent Owner's Response identified by UTC. We further determine that the Motion to Exclude is moot as to Exhibit 1017.

3. Rogers Declaration (Ex. 1022)

UTC seeks to exclude paragraphs 44–48 and 84–87 of the Rogers Declaration (Ex. 1022). PO Mot. Exclude 8–9. UTC asserts that paragraphs 44–48 constitute new opinions concerning the melting point of treprostinil diethanolamine salt Form A, and paragraphs 84–87 improperly rely on facts not in the record. *Id*.

SteadyMed responds that the paragraphs in question directly respond to UTC's challenges concerning the melting point of Phares treprostinil, and

that Dr. Rogers' opinions regarding the equipment used to generate Phares' data was proper. Pet. Opp. Exclude 8–9.

We are not persuaded by UTC's arguments. Dr. Rogers' testimony pertains directly to UTC's challenges on melting point. *See* Ex. 1022 ¶¶ 44–48, 84–87. Moreover, Dr. Rogers' reliance on personal knowledge concerning the instrumentation and software used by Phares is appropriate, because such knowledge is of the sort that a polymorph expert would rely on in providing opinions on compound purity. *See* Fed. R. Evid. 702, 703.

In addition, it is within our discretion to assign the appropriate weight to be accorded to evidence. In its motion, UTC has not explained adequately why we should exclude Dr. Rogers' testimony, instead of giving it little or no weight. *See, e.g.*, *Donnelly Garment Co.*, 123 F.2d at 224.

For the foregoing reasons, we decline to exclude any portion of the Rogers Declaration (Ex. 1022).

4. Williams Deposition Transcript (Ex. 2059)

UTC contends that "Petitioner's Reply to Patent Owner's Response includes a number of statements and references that misrepresent certain testimony from the deposition transcript of Dr. Williams (Ex. 2059)." PO Mot. Exclude 9. On this basis, UTC seeks to exclude several excerpts from Dr. Williams' deposition and corresponding portions of Petitioner's Reply to Patent Owner's Response. *Id*. at 9–10.

SteadyMed responds that "a motion to exclude is not a proper vehicle for a party to argue that the other

party's arguments are incorrect." Pet. Opp. Exclude 9 (quoting *Hopkins Manufacturing Co., v. Cequent Performance Products, Inc.*, IPR2015-00609, Paper 32, at *23 (PTAB July 28, 2016)). SteadyMed additionally asserts that UTC's arguments go to weight, not admissibility of the evidence. Lastly, SteadyMed points out that, with one exception, UTC failed to object to the disputed portions of Dr. Williams' testimony during his deposition. *Id*. at 10.

We are not persuaded by UTC's arguments. Rather, we agree with SteadyMed that a motion to exclude is not an appropriate means for expressing disagreement with an opposing party's arguments. We also agree with SteadyMed that any concerns regarding the mischaracterization or misrepresentation of Dr. Williams' testimony go to the weight attributable to, and not the admissibility of, that testimony and SteadyMed's arguments. We further observe that to the extent UTC did not object to the disputed questions during Dr. Williams' deposition, any objections to those questions have been waived.

In addition, it is within our discretion to assign the appropriate weight to be accorded to evidence.

For the foregoing reasons, we decline to exclude any portion of Petitioner's Reply to Patent Owner's Response (Paper 51), or the Deposition Transcript of Dr. Robert M. Williams, Ph.D. (Ex. 2059).

III. CONCLUSION

For the foregoing reasons, we determine that SteadyMed has shown by a preponderance of the evidence that claims 1–22 are unpatentable.

IV. ORDER

It is

ORDERED that claims 1–22 of the '393 patent are unpatentable;

FURTHER ORDERED that SteadyMed's Motion to Exclude Evidence is dismissed.

FURTHER ORDERED that UTC's Motion to Exclude Evidence is denied.

FURTHER ORDERED that, because this is a Final Written Decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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APPENDIX C

Paper _____

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Case IPR2016-00006

[Filed April 21, 2016]

STEADYMED LTD.,	)
	)
Petitioner,	)
	)
v.	)
	)
UNITED THERAPEUTICS CORPORATION,	)
	)
	)
Patent Owner.	)
	)

U.S. Patent No. 8,497,393
Issue Date: Jul. 30, 2013
Title: PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®

Case IPR2016-00006

JOINT WRITTEN STATEMENT

Mail Stop "PATENT BOARD"
Patent Trial and Appeal Board
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Pursuant to the Board's Order in Paper No. 14, United Therapeutics Corporation ("Patent Owner") and SteadyMed Ltd. ("Petitioner") hereby submit this Joint Written Statement identifying those parts of the Decision to Institute that should remain under seal, accompanied by a redacted copy of the Decision to Institute. Further, a joint motion to seal is filed concurrently herewith.

The portions of the Decision to Institute that are redacted and should remain under seal are as follows (the precise words being redacted are shown in the attached redacted copy of the Decision to Institute):

On page 17, lines 21-23;

On page 18, line 24;

On page 19, lines 1-4, 16-18, and 20-22;

On page 20, lines 1-17 and footnote 7; and

On page 21, lines 1-3 and 6-9.

Patent Owner and Petitioner conferred on April 18, 2016 concerning the specific scope of redactions presented in the attached redacted version of the Decision to Institute. After reviewing and discussing the proposed redactions, Petitioner has indicated that

it does not object to the scope of proposed redactions sought by Patent Owner in this filing.

Patent Owner therefore respectfully requests that the redacted portions of the Decision to Institute identified in this Joint Written Statement and accompanying redacted version of the Decision to Institute remain under seal.

Date: April 21, 2016 Respectfully submitted,

/s/ Stuart E. Pollack /
Stuart E. Pollack
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Counsel for Petitioner

/s/ Stephen B. Maebius
Stephen B. Maebius
Reg. No. 35,264
Counsel for Patent Owner

* * *

[*Certificate of Service Omitted in the Printing of this Appendix*]

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REDACTED
DECISION – INSTITUTION OF *INTER PARTES*
REVIEW

Trials@uspto.gov
571-272-7822

Paper No. 12
Entered: April 8, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

STEADYMED LTD.,

Petitioner,

v.

UNITED THERAPEUTICS CORPORATION,

Patent Owner.

Case IPR2016-00006
Patent No. 8,497,393 B2

Before LORA M. GREEN, JONI Y. CHANG, and JACQUELINE T. HARLOW, *Administrative Patent Judges.*

HARLOW, *Administrative Patent Judge.*

DECISION
Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

Petitioner, SteadyMed LTD ("SteadyMed"), filed a Petition requesting an *inter partes* review of claims 1–22 of U.S. Patent No. 8,497,393 B2 (Ex. 1001, "the '393 patent"). Paper 1 ("Pet."). Patent Owner, United Therapeutics Corporation ("UTC"), filed a Preliminary Response on January 14, 2016. Paper 10[1] ("Prelim. Resp."). We have jurisdiction under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted unless the information presented in the petition "shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition."

For the reasons set forth below, we institute an *inter partes* review of claims 1–22 of the '393 patent.

A. Related Matters

The '393 patent is asserted in: *United Therapeutics Corp. v. Sandoz, Inc.*, No. 14-cv-05499 (D.N.J.); *United Therapeutics Corp. v. Teva Pharmaceuticals U.S.A., Inc.*, No. 14-cv-05498 (D.N.J.); and *United Therapeutics Corp. v. Watson Laboratories, Inc.*, No. 15-cv-05723 (D.N.J). Pet. 1. SteadyMed is not party to the above identified litigations. *Id*.

B. The '393 Patent

The '393 patent, titled "Process to Prepare Treprostinil, the Active Ingredient in Remodulin®," issued July 30, 2013, from U.S. Patent Application No.

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[1] Paper 10 is the Unredacted Preliminary Response. Paper 8, filed concurrently with Paper 10, is a redacted version of the Preliminary Response.

13/548,446 ("the '446 application") (Ex. 1002), filed July 13, 2012. Ex. 1001, [54], [45], [21], [22]. The '446 application is a continuation of U.S. Patent Application No. 12/334,731 ("the '731 application") (Ex. 1002), filed on December 15, 2008, now issued as U.S. Patent No. 8,242,305 ("the '305 patent"). Ex. 1001, [63]. The '393 patent claims priority to U.S. Provisional Patent Application No. 61/014,232 (Ex. 2008), filed December 17, 2007. Ex. 1001, [60].

The '393 patent recites 22 product-by-process claims for prostacyclin derivatives, including treprostinil.[2] *Id*. at 17:51–21:16; Pet. 5; Prelim. Resp. 3. The process disclosed by the '393 patent takes advantage of carbon treatment and salt formation steps to remove impurities, eliminating the need for purification by column chromatography. *Id*. at 17:29–32; *see also id*. at 5:41–45 ("purification by column chromatography is eliminated . . . . [T]he salt formation is a much easier operation than column chromatography.").

The process for forming prostacyclin derivatives described in the '393 patent includes four steps: (a) alkylating a prostacyclin derivative to form an alkylated prostacyclin derivative; (b) hydrolyzing the alkylated prostacyclin derivative with a base to form a prostacyclin acid; (c) contacting the prostacyclin acid with a base to form a prostacyclin carboxylate salt; and (d) optionally reacting the prostacyclin carboxylate salt

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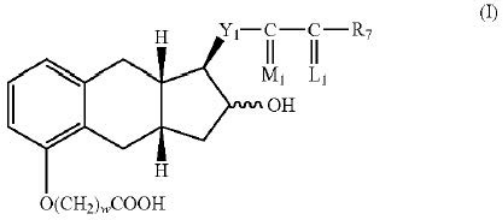
[2] The '305 patent, which issued from the parent to the application for the '393 patent, recites claims to a process for the preparation of prostacyclin derivatives comprising steps similar to those set forth in the product-by-process claims of the '393 patent. *Compare* Ex. 1001, 17:51–21:16, *with* Ex. 2007, 17:39–24:3.

formed in (c) with an acid to form the desired compound, or pharmaceutically acceptable salt thereof. *Id*. at 1:65–3:19.

C. Illustrative Claim

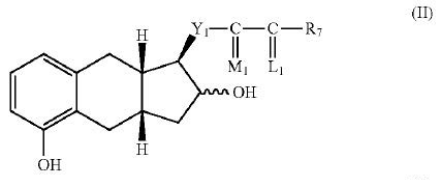
Each of the challenged claims is a product-by-process claim. Of the challenged claims, claims 1 and 9 are independent. Claim 1, reproduced below, is illustrative of the claimed subject matter.

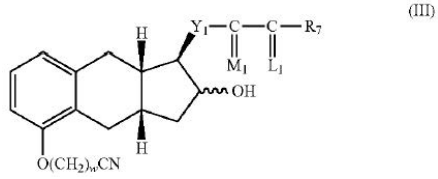
1. A product comprising a compound of formula I



or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising

a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III,

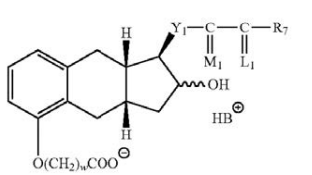




wherein [recitation of Markush groups for the specified structures],

b) hydrolyzing the product of formula III of step (a) with a base,

c) contacting the product of step (h)[3] with a base B to form a salt of formula I_s.



and

d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula I.

Ex. 1001, 17:51–19:29. Claim 9 is drawn to a product comprising a specific treprostinil compound within the genus set forth in claim 1, and made by the process recited in claim 1. *Id*. at 19:48–20:46.

D. Prior Art Relied Upon

SteadyMed relies upon the following prior art references (Pet. 4–6):

Phares	WO 2005/007081 A2	Jan. 27, 2005 (Ex. 1005)

[3] We note that the reference to "step (h)," rather than "step (b)," in claim 1 is an apparent typographical error. *See* Ex. 1001, 3:66–67 ("(c) contacting the product of step (b) with a base B to for a salt of formula IVs"); *see also* Pet. 25; Ex. 1009 ¶ 51.

Kawakami JP 56-122328A Sept. 25, 1981 (Ex. 1006)[4]

Moriarty et al., *The Intramolecular Asymmetric Pauson-Khand Cyclization as a Novel and General Stereoselective Route to Benzindene Prostacyclins: Synthesis of UT-15 (Treprostinil)*, 69 J. Org. Chem. 1890–1902 (2004) ("Moriarty") (Ex. 1004); and

Seyhan N. Eğe, ORGANIC CHEMISTRY 543–547 (2d ed. 1989) ("Eğe") (Ex. 1008).

E. Asserted Grounds of Unpatentability

SteadyMed asserts the following grounds of unpatentability (Pet. 3–4):

Claims	Basis	Reference(s)
1–5, 7–9, 11–14, and 16–20	§ 102(b)	Phares
1–5, 7–9, 11–14, and 16–20	§ 103(a)	Moriarty and Phares or Kawakami
6, 10, 15, 21, and 22	§ 103(a)	Moriarty, Phares, Kawakami, and Eğe

[4] SteadyMed submitted a certified English translation of Kawakami as Ex. 1007. As discussed in Part II.F below, UTC argues the admissibility of this translation.

II. ANALYSIS

A. 35 U.S.C. § 325(d)

UTC urges the exercise of our discretion under 35 U.S.C. § 325(d) to deny some or all of the grounds of unpatentability presented by SteadyMed because the same, or substantially similar issues were addressed during prosecution. Prelim. Resp. 25–26. UTC states that the Patent Office considered Moriarty alone, and in combination with Phares, during prosecution of the '393 patent. *Id*. at 8–10, 26. UTC also reports that Phares was considered alone, and in combination with Moriarty, during prosecution of U.S. Patent Application No. 13/910,583 ("the '583 application") (Ex. 2010) filed June 5, 2013, which is a continuation of the '446 application. *Id*. at 11–14.

Regarding the patentability of claims 6, 15, 21, and 22, in particular, UTC asserts that Eğe "is nothing more than a first-year organic chemistry textbook," and that SteadyMed "relies on nothing more than conclusory statements in three paragraphs of the [Declaration of Jeffery D. Winkler]" to support its unpatentability arguments. *Id*. at 26. UTC therefore contends that SteadyMed "has provided no evidence of probative value that is any different than what was already before the Patent Office during prosecution." *Id*. at 26–27.

Although it is within our discretion to "reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office" pursuant to 35 U.S.C. § 325(d), we decline to do so here.

We note that during prosecution of the '446 application, which issued as the '393 patent, the Examiner rejected the claims as anticipated by Moriarty, but subsequently withdrew that rejection, without elaboration, in response to a declaration filed by David A. Walsh ("Walsh Declaration") (Ex. 1002, 346–350), one of the named inventors of the '393 patent, and the Executive Vice President of Chemical Research and Development at UTC. Ex. 1002, 344, 346–360. Although Phares is listed as a cited reference on the face of the '393 patent (Ex. 1001, [56]), we observe that the Examiner neither relied on, nor otherwise discussed Phares during prosecution of the '446 application (Ex. 1002, 295–296, 327–330, 359). In addition, neither Eğe nor Kawakami was considered during prosecution of the '446 application. *Id*. at 235–359. The grounds of unpatentability asserted in the instant Petition likewise differ from the rejections entered by the Examiner during prosecution of the '731 application, the parent to the '446 application. *See* Ex. 1002, 122–124.

Moreover, as discussed in detail in Part II.B below, the Declaration of Jeffrey D. Winkler ("Winkler Declaration") (Ex. 1009), submitted in support of SteadyMed's Petition, calls into question Dr. Walsh's conclusion that treprostinil prepared according to the process claimed in the '393 patent is "physically different from treprostinil prepared according to the process of 'Moriarty'" (Ex. 1002, 347 (¶ 6)). Ex. 1009 ¶¶ 63–71. In addition, as set forth in Part II.F, we disagree with UTC's characterization of Dr. Winkler's testimony as conclusory. *See, e.g.,* Ex. 1009 ¶¶ 80–90.

We, therefore, decline to exercise our discretion to deny the Petition pursuant to 35 U.S.C. § 325(d). *See Nestle USA, Inc. v. Steuben Foods, Inc.*, Case IPR2014-01235, slip op. at 7 (PTAB Dec. 22, 2014) (Paper 12) ("[W]e conclude that Petitioner's arguments regarding the unpatentability of claims 18–20, which include arguments relating to Biewendt and a combination of references previously not considered and supported by a declaration previously not considered, are persuasive. . ."); *Merial Ltd., v. Virbac*, Case IPR2014-01279, slip op. at 9 (PTAB Jan. 22, 2015) (Paper 13) (noting the different burdens of proof and evidentiary standards applicable to *ex parte* examination and *inter partes review* proceedings).

B. Claim Construction

In an *inter partes* review, claim terms in an unexpired patent are given their broadest reasonable interpretation in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *see also In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1278–79 (Fed. Cir. 2015) ("Congress implicitly approved the broadest reasonable interpretation standard in enacting the AIA," and "the standard was properly adopted by PTO regulation."), *cert. granted sub nom. Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 890 (2016) (mem.). Under this standard, we may take into account definitions or other explanations provided in the written description of the specification. *In re Morris*, 127 F.3d 1048, 1054 (Fed. Cir. 1997). Any special definition for a claim term must be set forth in the specification with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994). Only those terms that are in controversy

need be construed, and only to the extent necessary to resolve the controversy. *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999).

"Product" / "A product comprising a compound [of/having] formula [I/IV] . . . or a pharmaceutically acceptable salt thereof"

Independent claims 1 and 9 recite the phrase "[a] product comprising a compound [of/having] formula [I/IV] . . . or a pharmaceutically acceptable salt thereof . . . ." Ex. 1001, 19:48–20:46. In addition, each challenged dependent claim recites the term "product." *Id*. at 17:51–21:16. Because the parties advance similar arguments pertaining to the construction of these terms, we address these terms together.

SteadyMed asserts that the phrase "[a] product comprising a compound [of/having] formula [I/IV] . . . or a pharmaceutically acceptable salt thereof" should be interpreted to mean "a chemical composition that includes, but is not limited to, a compound of Formula I, or a pharmaceutically acceptable salt thereof, and that may also include other non-mentioned substances (including impurities), additives, or carriers, without limitation as to the types or relative amounts thereof." Pet. 11. SteadyMed contends that because independent claims 1 and 9 recite "[a] product comprising," the claim term "product" should be construed to include "the treprostinil compound along with other substances (including impurities)," i.e., a "chemical composition." *Id*. at 11.

UTC counters that "[a] product comprising a compound [of/having] formula [I/IV] . . . or a pharmaceutically acceptable salt thereof" should be

interpreted as "a substance resulting from a chemical reaction constituted primarily of formula I/IV or a pharmaceutically acceptable salt thereof." Prelim. Resp. 21. As an initial matter, UTC notes that SteadyMed's proposed construction refers only to Formula I, and asserts that SteadyMed "inexplicably read[s] Formula IV out of the term entirely." *Id*. at 22.

UTC further argues that the claims and Specification of the '393 patent use "product" to refer to a substance resulting from a chemical reaction. *Id*. at 17. UTC also contends that the prosecution history for the '393 patent supports its proposed construction because "during prosecution, the Patent Owner and Examiner explicitly discussed the 'product' of the claims as a real world substance that results from employing a specific chemical process, as differentiated from the substance obtained from employing a different chemical process." *Id*. at 18–19. UTC points to chemistry textbooks as buttressing its position that a skilled artisan would understand the claim term "product" as referring to "a substance resulting from a chemical reaction." *Id*. at 19. UTC further reasons that "the 'product' claimed in a product-by-process claim is necessarily a substance that results from the process specified in that claim" (*id*.), and that SteadyMed's proposed construction "contradicts this inherent limitation of the claims" (*id*. at 22).

On this record, and for purposes of this decision, we interpret the phrase "[a] product comprising a compound [of/having] formula [I/IV] or a pharmaceutically acceptable salt thereof," to mean "a product including, but not limited to, a compound

[of/having] formula [I/IV] or a pharmaceutically acceptable salt thereof."

The claim term "product," as it is used in the '393 patent, does not require construction because the claimed "product" is defined by the limitations recited in the challenged claims. This is evidenced by independent claims 1 and 9, which recite "[a] product comprising . . . ," and go on to define the essential elements of the claimed product. The transitional term "'comprising' is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim." *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501 (Fed. Cir. 1997); *see also* Ex. 1001, 4:23–25 (defining "comprising" as "including, but not limited to"). Thus, the open-ended structure of the challenged claims forecloses limitation of the term "product" beyond that achieved by the recited claim elements.

Indeed, neither UTC nor SteadyMed identifies any disclosure in the '393 patent or its prosecution history that necessitates a contrary understanding of the term "product." For example, the portions of the Specification to which UTC points comport with an understanding of "product" as being defined only by the recited claim elements. *See* Ex. 1001, 5:45–46, 7:16–20, 17:37–40. Furthermore, far from disavowing or otherwise limiting claim scope, the portions of the prosecution history identified by UTC are consistent with an understanding that the claimed "product" is defined solely by the recited claim elements. *See* Ex. 1002, 315, 328–329, 346–350. We similarly are unpersuaded that the chemistry textbook glossaries to

which UTC points (Exs. 2011, 2012, 2014) provide a basis for narrowly interpreting "product" to require that the product result from a chemical reaction.

Regarding the larger claim phrase "[a] product comprising a compound [of/having] formula [I/IV] . . . or a pharmaceutically acceptable salt thereof," as explained above, we determine that the embedded claim term "comprising" means "including, but not limited to." *See Genentech*, 112 F.3d at 501; *see also* Ex. 1001, 4:23–25. Accordingly, we reject UTC's proposal that claims 1 and 9 be read to require a product "*constituted primarily of* formula I/IV or a pharmaceutically acceptable salt thereof." Prelim. Resp. 21 (emphasis added).

"[A/the] process comprising"

SteadyMed argues that the claim phrase "[a/the] process comprising," which appears in independent claims 1 and 9, should be interpreted as "a process that includes, but is not limited to, the recited process steps, and may include, without limitation, any other non-recited steps." Pet. 12. UTC counters that this claim phrase should be construed to mean "a/the process including but not limited to." Prelim. Resp. 23–24. For the reasons set forth above, we agree with UTC that these claim phases should be interpreted to mean "a/the process including, but not limited to."

Product-by-Process Claims

Each of the challenged claims is a product-by-process claim. Ex. 1001, 17:51–21:16; Pet. 5; Prelim. Resp. 3. The general rule when determining patentability of a product-by-process claim is to "focus . . . on the product and not on the process of making it."

Amgen, Inc. v. Hoffman-La Roche Ltd., 580 F.3d 1340, 1369 (Fed. Cir. 2009). This general rule embodies the long-standing principle that "an old product is not patentable even if it is made by a new process." *Id*. at 1370. An exception applies when process steps recited in the claim impart "structural and functional differences" to the claimed product. *Greenliant Sys., Inc. v. Xicor LLC*, 692 F.3d 1261, 1267–1268 (Fed. Cir. 2012). If the exception applies, the structural and functional differences conveyed by the recited process steps "'are relevant as evidence of no anticipation' although they 'are not explicitly part of the claim.'" *Id*. at 1268 (citing *Amgen*, 580 F.3d at 1370).

SteadyMed contends that the challenged claims do not yield a treprostinil product having structural or functional differences as compared to treprostinil products produced by prior art methods. Pet. 19–22. Specifically, SteadyMed asserts that the Walsh Declaration, relied on by UTC during prosecution as evidencing differences in the treprostinil products of the '393 patent and Moriarty, fails to demonstrate any functional or structural differences between the instantly claimed and prior art treprostinil products. *Id*. SteadyMed relies on the Winkler Declaration (Ex. 1009) to support its position. *Id*.

UTC acknowledges that "at the time of the '393 patent, there existed at least three prior art methods" for making treprostinil. Prelim. Resp. 33. Relying on the Walsh Declaration, UTC asserts that the process steps recited in independent claims 1 and 9 are entitled to patentable weight because they yield a "physically different and improved final product with significantly reduced overall impurities and a distinct and

unexpected impurity profile" as compared to treprostinil produced using prior art methods. *Id*. at 3.

The Walsh Declaration compares the impurity profile of treprostinil free acid "prepared according to the process of 'Moriarty'" to the impurity profiles of treprostinil free acid and treprostinil diethanolamine "prepared according to the process specified in claim 1 or [9]" of the '393 patent.[5] Ex. 1002, 347–348 (¶ 6). Dr. Walsh concludes that the treprostinil free acid and treprostinil diethanolamine prepared according to the process of claims 1 and 9 is physically different from the treprostinil diethanolamine prepared according to the process of Moriarty "at least because neither of [the '393 patent products] contains a detectable amount of any of benzindene triol, treprostinil methyl ester, 1AU90 treprostinil stereoisomer and 2AU90 treprostinil stereoisomer, each of which were present in detectable amounts in treprostinil produced according to the process of 'Moriarty'." *Id*. at 349 (¶ 8). In addition, Dr. Walsh provides "data obtained from representative Certificates of Analysis" indicating that treprostinil free acid "prepared according to 'Moriarty'" is 99.4% pure, while the treprostinil free acid and treprostinil diethanolamine "prepared according to the process specified in claim 1 or [9]" are 99.8% pure and 99.9% pure, respectively. *Id*. at 347–348 (¶ 6).

SteadyMed disputes Dr. Walsh's contention that there are physical differences between the treprostinil products of the '393 patent and prior art. Pet. 19–22;

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[5] Issued claim 9 of the '393 patent is identified as claim 10 in the Walsh Declaration, and other documents in the prosecution history in the '393 patent.

see also Ex. 1009 ¶¶ 63–71. As an initial matter, SteadyMed points out that the 99.7% treprostinil purity reported by Moriarty (Ex. 1004, 13) is higher than the 99.5% purity recited in claims 2 and 10 of the '393 patent, the only challenged claims that recite a purity level. Pet. 20; *see also* Ex. 1009 ¶ 65. In addition, Dr. Winkler testifies that the limited sample set, consisting of "*only two specific batches* of treprostinil" (Ex. 1009 ¶ 66), and absence of any disclosure concerning the reaction conditions, reagents, and solvents used in carrying out the process of claims 1 and 9 of the '393 patent (*id*. ¶ 67), undermine the veracity of Dr. Walsh's conclusion regarding the purity of these products. *Id*. ¶¶ 66–67. SteadyMed also observes that the statement in the Specification of the '393 patent that in one embodiment the purity of treprostinil is "at least 90.0%, 95.0%, 99.0%, 99.5%" (Ex. 1001, 8:66–67), supports the conclusion that the 99.8% purity purportedly achieved by Dr. Walsh "is based on a particular set of process steps that are not claimed and which must have been found after the filing date." Pet. 20.

Dr. Winkler additionally testifies that the alleged differences in purity between the treprostinil batches described by Dr. Walsh are attributable to experimental error. *Id*. ¶¶ 68–70. Dr. Winkler testifies that "the literature on [High Performance Liquid Chromatography's ("HPLC's")] precision indicates that the 'RSD' or 'relative standard deviation' for a typical instrument is about 1%. (Ex. 1017.)." *Id*. ¶ 70. Dr. Winkler further observes that "[i]n the present case, we can estimate the precision of the equipment the inventors actually used, since the inventors found that Example 4's Batch 1 had an HPLC Assay of 100.4%,

which is obviously greater than the 100% value theoretically achievable. (Ex. 1001, col. 13, lines 50-65)." *Id*. Dr. Winkler, thus, concludes that "[t]his deviation between experimental and theoretical shows that the instrument can have variations of at least 0.4%, which is greater than the differences in purity that the inventors offered to support their contention regarding greater purity over the prior art." *Id*. On this record, we credit Dr. Winkler's testimony, as it is consistent with the disclosures of the prior art and the disclosure of the '393 patent itself.

UTC does not challenge SteadyMed's arguments concerning the shortcomings of the Walsh Declaration. Rather, UTC points to correspondence with, and reports submitted to, the Food and Drug Administration ("FDA") relating to the acceptance of a supplemental new drug application for treprostinil. Prelim. Resp. 36–38. UTC contends that these reports show that "[redacted] Prelim. Resp. 38; *see also* Ex. 2006, 3–4.

On the record before us, and for purposes of this decision, we conclude that the process steps recited in the challenged claims do not impart structural or functional differences to the claimed product.

As an initial matter, we observe that the challenged product-by-process claims are drawn to "[a] product comprising a compound" of either formula I or formula IV, or a pharmaceutically acceptable salt of the recited formula. Ex. 1001, 17:51–19:29, 19:48–20:46). "'Comprising' is a term of art used in claim language which means that the named elements are essential,

but other elements may be added and still form a construct within the scope of the claim." *Genentech*, 112 F.3d at 501. Thus, a product comprising a particular compound must contain that compound, but may additionally include other substances, such as impurities. On this record, therefore, it is unclear how claims 1, 3–9, and 11–22, which claim a product comprising a particular compound, but do not recite limitations concerning the purity profile of that product, could be restricted to a product including the claimed compound, but also having a particular purity profile. In addition, although claims 2 and 10 require a purity of at least 99.5% (Ex. 1001, 19:29–30, 20:47–48), these claims similarly are drawn to a product comprising a compound, and do not specify the type of impurities that may be present in the compound or restrict the amount of any particular impurity that may be present, so long as the product remains at least 99.5% pure.

Furthermore, the evidence presently before us, including UTC's own testing results, suggests that [redacted] We observe that UTC offers no explanation for the variation between the 99.7% purity reported by Moriarty, and the 99.4% purity Dr. Walsh obtained for treprostinil purportedly prepared according to the process described by Moriarty. Neither does UTC offer reasoning for crediting Dr. Walsh's results over those reported by Moriarty himself. Similarly, UTC neglects Dr. Winker's assessment of the experimental error present, but unaccounted for, in the impurity measurements reported in the Walsh Declaration, and fails to account

for the absence of any disclosure regarding the experimental protocols followed by Dr. Walsh, such as the reaction conditions, or the solvents or reagents used, in synthesizing treprostinil according to Moriarty or the '393 patent.

Moreover, the Process Optimization Report (Ex. 2005) proffered by UTC supports the conclusion that [redacted]

The Process Optimization Report discloses the impurity analyses for five batches of treprostinil identified by UTC [redacted]. Ex. 2005, 4–6; *see also* Prelim. Resp. 36 ("[redacted]

[redacted]

[6] We note that UTC likely intended to reference independent claim 9 of the '393 patent, rather than dependent claim 10; however our analysis is equally applicable to claim 9 or claim 10.

[7] [redacted]

[redacted] Notably, UTC's specification for treprostinil produced according to the '393 patent permits each of the following impurities: [redacted]. Ex. 2006, 6. The analysis of treprostinil purportedly prepared according to the process of Moriarty, set forth in the Walsh Declaration, reveals that each of the impurities detected in Moriarty treprostinil was present in an amount [redacted] *Compare* Ex.1002, 347, *with* Ex. 2006, 6.

Accordingly, on the record before us, and for purposes of this decision, we conclude that the process steps recited in the challenged claims of '393 patent do not impart structural or functional differences to the claimed product as compared to prior art processes, and therefore, that these process steps do not patentably limit the claimed product. We note, however, that the factual dispute between the parties concerning the existence of any structural or functional differences between treprostinil products produced according to the process recited in the '393 patent and prior art processes, as well as arguments addressing our concerns regarding the relevance of the impurity profile of a product obtained by the recited process to the patentability of claims drawn to a product *comprising* a compound, are appropriate for further development at trial.

C. Principles of Law

To establish anticipation, each and every element in a claim, arranged as recited in the claim, must be found in a single prior art reference. *Net MoneyIN, Inc. v. VeriSign, Inc*., 545 F.3d 1359, 1369 (Fed. Cir. 2008). "A reference anticipates a claim if it discloses the claimed invention 'such that a skilled artisan could take its teachings in combination with his own knowledge of the particular art and be in possession of the invention.'" *In re Graves*, 69 F.3d 1147, 1152 (Fed. Cir. 1995) (emphasis omitted) (quoting *In re LeGrice*, 301 F.2d 929, 936 (CCPA 1962)).

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *KSR Int'l Co. v. Teleflex Inc*., 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

> When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability. For the same reason, if a technique has been used to

> improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill. *Sakraida* [*v. Ag Pro, Inc.*, 425 U.S. 273 (1976)] and *Anderson's–Black Rock* [*v. Pavement Salvage Co.*, 396 U.S. 57 (1969)] are illustrative—a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions.

KSR, 550 U.S. at 417.

The level of ordinary skill in the art is reflected by the prior art of record. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001); *In re GPAC Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995); *In re Oelrich*, 579 F.2d 86, 91 (CCPA 1978).

D. Anticipation Grounds of Unpatentability Based on Phares

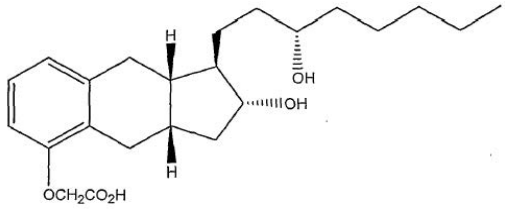
SteadyMed asserts that claims 1–5, 7–9, 11–14, and 16–20 are unpatentable under § 102(b) as anticipated by Phares. Pet. 22–37. Claims 2–5, 7, 8, and 19 depend directly from claim 1, and claims 11–14, 16–18, and 20 depend, directly or indirectly, from claim 9. In support of its assertion, SteadyMed provides detailed explanations as to how Phares discloses each claim limitation (*id.*), and relies upon the Winkler Declaration (Ex. 1009) to support its positions.

UTC counters that the treprostinil product of Phares is physically different from that produced by the process disclosed in the '393 patent, and, therefore, that the process steps disclosed in the claims of the '393

patent are limiting for purposes of the patentability determination. Prelim. Resp. 33–36. UTC also argues that SteadyMed improperly engages in picking and choosing among distinct embodiments in Phares to piece together an anticipation argument as to the recited process steps. *Id*. at 29–31. UTC further asserts that explicit disclosure of certain claimed process steps is absent from SteadyMed's anticipation analysis, and that SteadyMed fails to show that those limitations are inherently disclosed by Phares. *Id*. at 31–36.

Phares

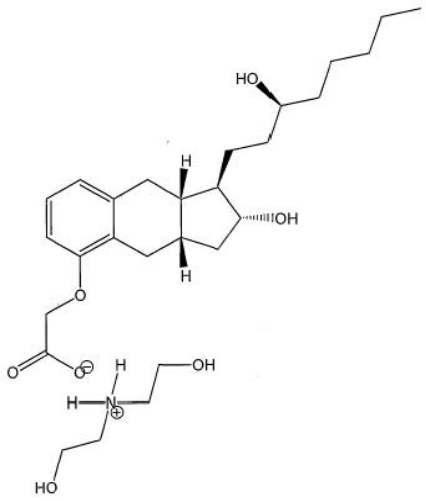
Phares describes "compounds and methods for inducing prostacyclin-like effects in a subject or patient," including treprostinil and derivatives thereof. Ex. 1005, 10. The chemical structure of treprostinil disclosed by Phares, on page 10 of Exhibit 1005, is reproduced below:



Id. Phares explains that "[t]reprostinil is a chemically stable analog of prostacyclin, and as such is a potent vasodilator and inhibitor of platelet aggregation." *Id*.

Phares further discloses that "[a] preferred embodiment of the present invention is the diethanolamine salt of treprostinil. . . . A particularly preferred embodiment of the present invention is form B of treprostinil diethanolamine." *Id*. at 11. The

structure of the diethanolamine salt of treprostinil described by Phares, on page 99 of Exhibit 1005, is reproduced below:

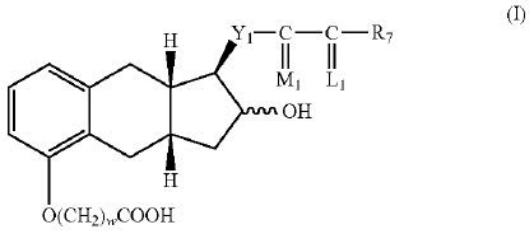


Id. at 99 (claim 49). Phares reports that form B of the diethanolamine salt of treprostinil "appears to be a crystalline material which melts at 107°C." *Id*. at 91.

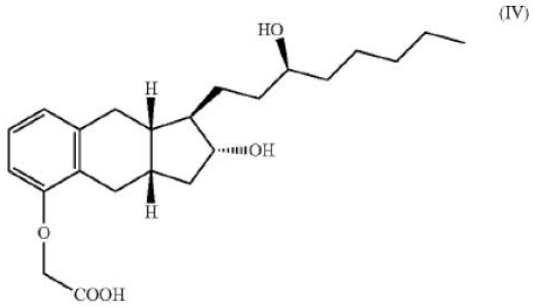
Phares describes the synthesis of (-)-treprostinil, the enantiomer of treprostinil. Ex. 1005, 41–42. Phares explains that "[e]nantiomers of these compounds . . . can be synthesized using reagents and synthons of enantiomeric chirality of the above reagents." *Id*. at 41. In particular, Phares teaches that "the enantiomer of the commercial drug (+)-Treprostinil was synthesized using the stereoselective intramolecular Pauson Khand reaction as a key step and Mitsunobu inversion of the side-chain hydroxyl group." *Id*. at 42. Phares discloses the following reaction procedure: "i. $ClCH_2CN$, K_2CO_3. ii, KOH, CH_3OH, reflux. 83 % (2 steps)." *Id*.

A product comprising a compound [of/having] formula [I/IV] . . . or a pharmaceutically acceptable salt thereof

Claim 1 of the '393 patent recites "[a] product comprising a compound of formula I



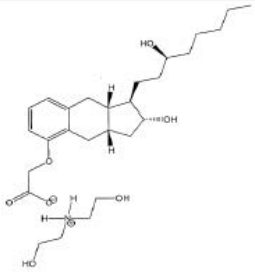
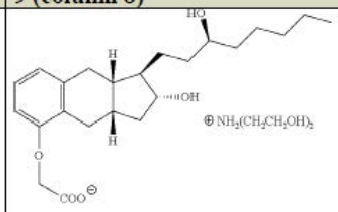
or a pharmaceutically acceptable salt thereof," and sets forth a series of process steps for obtaining the claimed product. Claim 9 recites "[a] product comprising a compound having formula IV



or a pharmaceutically acceptable salt thereof," and includes the same process steps for obtaining the claimed product as recited in claim 1. Claim 9 is identical to claim 1, except that it is drawn to a product comprising the specific treprostinil compound, a species of the genus of claim 1. Accordingly, we address these claims together.

SteadyMed contends that "Phares discloses in its Claim 49 the identical, pharmaceutically acceptable treprostinil diethanolamine salt" claimed in the '393 patent. Pet. 26; *see also* Ex. 1005, 24, 85–93, 99 (claim 49); Ex. 1009 ¶¶ 50–53. In support of SteadyMed's position, Dr. Winkler testifies that "[o]ther than a change in formatting, the two structures [for treprostinil diethanolamine salt] from Phares and the '393 Patent are identical." Ex. 1009 ¶ 53.

Paragraph 52 of the Winkler Declaration depicts a side-by-side comparison of the chemical structures disclosed in claim 49 of Phares, and column 8, lines 50–63 of the '393 patent, reproduced below:

Phares (Ex. 1005), Claim 49	'393 Patent (Ex. 1001), Claims 1 & 9 (column 8)
	

Id. ¶ 52. As shown in the figure from paragraph 52 of the Winkler Declaration, the treprostinil diethanolamine salt disclosed by Phares is structurally identical to that disclosed in the '393 patent.

As set forth in Part II.B above, SteadyMed, relying on the Winkler Declaration, further asserts that the process disclosed in claims 1 and 9 of the '393 patent does not result in a treprostinil product that is physically different or unique from treprostinil

produced by prior art methods. Pet. 19–22; *see also* Ex. 1009 ¶¶ 63–71. In support of this position, Dr. Winkler testifies that "[i]n both the '393 Patent and Phares (Ex. 1005), treprostinil diethanolamine salt Form B is made . . . . Phares further discloses a melting point of 107° C (Ex. 1005, p. 91 & Fig. 21) for the Form B salt." Ex. 1009 ¶ 59; *see also* Ex. 1005, 90–93; Pet. 27. Dr. Winkler also testifies that Phares discloses the same procedure as is claimed in the '393 patent, but describes this procedure in reference to the synthesis of the enantiomer of treprostinil. Ex. 1009 ¶¶ 55–57; Ex. 1005, 41–42; Pet. 25–26. Dr. Winkler thus concludes that in "making the most stable crystal form (Form B) and preparing a product that melts at a higher temperature higher than that described in the '393 Patent, Phares necessarily discloses a salt of at least equal purity to the salt in the '393 Patent." Ex. 1009 ¶ 62; *see also id*. ¶ 60 (citing Ex. 1018, 6); Pet. 27–28.

SteadyMed also contends that Phares anticipates the process steps recited in claim 1. Pet. 24–28; Ex. 1005, 24, 41–42, 85–93, 99 (claim 49); Ex. 1009 ¶¶ 44–71.

UTC does not dispute Phares' disclosure of a treprostinil product; rather, as previewed in relation to its claim construction arguments above, UTC contends that the treprostinil product of Phares is "physically different" from that claimed in the '393 patent, and, therefore, not anticipatory. Prelim. Resp. 33–36. UTC argues that as Phares does not disclose which treprostinil starting material is used, it "cannot inherently anticipate the final treprostinil product of the '393 patent because each method would result in a distinct impurity profile." Prelim. Resp. 34. Referring

to the Walsh Declaration, UTC further asserts that "even if the Moriarty treprostinil was used for Phares, Petitioner has failed to provide any evidence that the final Phares treprostinil product would necessarily be the same as the products claimed in the '393 patent." *Id*. UTC also asserts that SteadyMed's reliance on the melting point of the treprostinil product of Phares as a proxy for purity is misplaced because "melting point does not disclose any specific impurity level and instead may demonstrate a different form, or polymorph, of treprostinil diethanolamine altogether." *Id*. at 35.

UTC additionally argues that Phares does not disclose the same process for generating treprostinil as recited in claims 1 and 9, and that SteadyMed improperly "cobbles together disclosure from four disparate portions of Phares covering multiple distinct embodiments" to arrive at the claimed invention. Prelim. Resp. 27. Further, UTC asserts that even if SteadyMed were permitted to pick and choose steps from various embodiments of Phares, SteadyMed nevertheless must rely on inherency to prove anticipation because "Phares lacks express disclosure of certain claim elements." *Id*. at 28.

The present record supports SteadyMed's contention that the treprostinil diethanolamine salt taught by Phares is identical in structure to the pharmaceutically acceptable treprostinil diethanolamine salt recited in claims 1 and 9. Pet. 24; *see also* Ex. 1005, 24, 99 (claim 49); Ex. 1009 ¶¶ 52–53. Dr. Winkler testifies that the process for producing treprostinil disclosed by Phares yields the same form (Form B) of treprostinil diethanolamine salt as the

process of the '393 patent, and that the treprostinil diethanolamine salt of Phares is at least equal in purity to the treprostinil product of the '393 patent. Ex. 1009 ¶¶ 59–62. Dr. Winkler further testifies that Phares discloses the same process for synthesizing treprostinil as the '393 patent. Ex. 1009 ¶¶ 55–57, 62; Ex. 1005, 41–42; Pet. 25–26. On this record, we credit Dr. Winkler's testimony.

We are not persuaded by UTC's arguments concerning the possibility that treprostinil produced according to Phares might have a different impurity profile than that produced according to the process disclosed in the '393 patent. First, for the reasons set forth in Part II.B above, it is unclear on this record how the use of the transitional phrase "comprising" excludes any impurities that may possibly be produced by the process of Phares. In addition, the present record supports a finding that the impurity profiles for treprostinil diethanolamine salt prepared as described by Phares and that prepared according to the '393 patent are the same. As explained above, Dr. Winkler's testimony regarding the form and melting point of Phares' treprostinil product, is consistent with the conclusion that the products of Phares and the '393 patent are the same.

Furthermore, we note that, as explained in Parts II.A and II.B above, the inter-batch variability in treprostinil impurity profiles, experimental error inherent in impurity measurements, and the variety and extent of impurities permitted in UTC's specification for the manufacture of treprostinil according to the process of the '393 patent, which remained unchanged when UTC migrated from a prior

art process to the process of the '393 patent, support the conclusion that the process steps recited in claims 1 and 9 of the '393 patent do not impart any structural or functional differences over prior art treprostinil products.

Accordingly, given the evidence before us in this record, we conclude that SteadyMed has established adequately for purposes of this decision that Phares teaches the treprostinil diethanolamine salt product recited in claims 1 and 9. Because we determine, on the record before us, and for purposes of this decision, that the process steps recited in claims 1 and 9 do not impart structural or functional differences to the claimed treprostinil product and are therefore not limiting, we do not address the parties' contentions concerning Phares' anticipation of the recited process steps.

Conclusion

UTC has not raised any additional arguments with regard to the dependent claims other than those addressed above. We have reviewed SteadyMed's evidence, arguments, and claim charts, and conclude that SteadyMed has sufficiently demonstrated that the dependent claims are also anticipated by Phares. Thus, for the foregoing reasons, we conclude that SteadyMed has shown a reasonable likelihood of prevailing on its assertions that claims 1–5, 7–9, 11–14, and 16–20 are anticipated by Phares.

E. Obviousness Grounds of Unpatentability Based on Moriarty and Phares

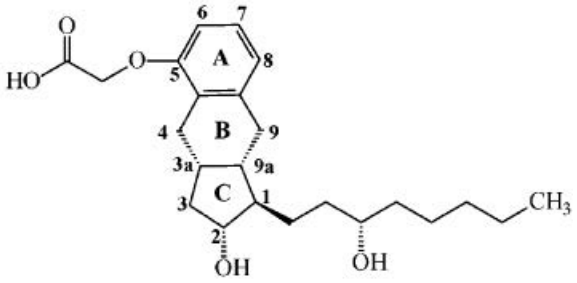
SteadyMed asserts that claims 1–5, 7–9, 11–14, and 16–20 are unpatentable under § 103(a) as obvious in

view of Moriarty and Phares. Pet. 37–52. Claims 2–5, 7, 8, and 19 depend directly from claim 1, and claims 11–14, 16–18, and 20 depend, directly or indirectly, from claim 9. In support of its assertion, SteadyMed provides detailed explanations as to how the combination of Moriarty and Phares discloses each claim limitation (*id*.), and relies upon the Winkler Declaration (Ex. 1009) to support its positions.

UTC counters that "Phares fails to disclose the synthetic route or purity of the claimed treprostinil product. Moriarty adds nothing to cure these deficiencies." Prelim. Resp. 43. UTC asserts that the process described in the '393 patent "unexpectedly reduced the impurity level in the claimed treprostinil product even more" than Moriarty, and reiterates its position that treprostinil produced according to the process of the '393 patent has "a superior purity profile compared to the prior art." *Id*. at 44.

Moriarty

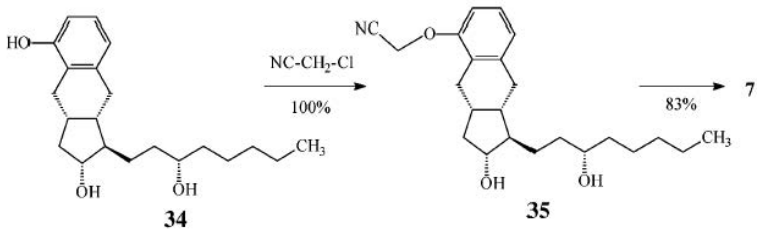
Moriarty describes the synthesis of treprostinil "via the stereoselective intramolecular Pauson-Khand cyclization." Ex. 1004, 1. Formula 7 of Moriarty is reproduced below:



7

Id. at 3. Formula 7 of Moriarty depicts the chemical structure of treprostinil. *Id*.

An excerpt of Scheme 4 of Moriarty is reproduced below:



Id. at 6. The excerpted portion of Scheme 4 of Moriarty illustrates the alkylation Formula 34 to yield Formula 35, and subsequent hydrolysis of Formula 35 with a base (followed by acidification) to yield Formula 7, treprostinil. Ex. 1004, 6, 13.

A product comprising a compound [of/having] formula [I/IV] . . . or a pharmaceutically acceptable salt thereof

SteadyMed contends that Moriarty and Phares respectively disclose treprostinil acid and treprostinil diethanolamine salt, as recited in claims 1 and 9 of the '393 patent. Pet. 22–23, 24, 33, 39, 48; *see also* Ex. 1004, 6, 13; Ex. 1005, 24, 99 (claim 49); Ex. 1009 ¶¶ 74, 76. Furthermore, Dr. Winkler testifies that the combination of Moriarty and Phares "discloses the same process steps and same product of the '393 Patent. For the same reasons discussed above regarding Phares, the purity of the combinations would be of at least equal purity to that claimed in the '393 Patent." Ex. 1009 ¶ 76.

SteadyMed asserts that Moriarty discloses steps (a) and (b) of claims 1 and 9, and that Phares discloses step (c) of these claims. Pet. 43; *see also* Ex. 1004, 6, 13; Ex. 1005, 24; Ex. 1009 ¶ 74. Dr. Winkler testifies that a relevant skilled artisan would have recognized that the treprostinil acid produced in Moriarty could be purified by contacting it with a base as described by Phares. Ex. 1009 ¶ 74. In addition, as discussed in Part II.D above, Dr. Winkler testifies that Phares "details the same Claim 1 and 9 steps (a) or (b) as were used to make treprostinil in the '117 Patent and Moriarty reference, but applies them to make (-)-treprostinil, the enantiomer of (+)- treprostinil (Ex. 1005, p. 42)." *Id*. ¶55. Dr. Winkler further testifies that a relevant skilled artisan would have had "more than a reasonable expectation of success that the reaction of treprostinil with diethanolamine would be successful" because "Phares (Ex. 1005, p. 24, p. 99, Claim 49) performed the same reaction and it was successful." Ex. 1009 ¶ 80.

UTC reasserts the arguments described above concerning the purity of treprostinil produced according to the process disclosed in the '393 patent. UTC acknowledges that Moriarty itself was an improvement over the prior art, but contends that "the '393 patent unexpectedly reduced the impurity level in the claimed treprostinil product even more." Prelim. Resp. 44. Specifically, UTC contends that "performing step (c) on a product that resulted from steps (a) and (b) provided a product with reduced impurities." *Id*. UTC also reiterates its arguments concerning the Walsh Declaration, and highlights the purported differences in the impurity profile of treprostinil

produced according to Moriarty compared to that produced according to the '393 patent.

The present record supports SteadyMed's contention that the treprostinil diethanolamine salt disclosed by the combination of Moriarty and Phares is identical in structure to the pharmaceutically acceptable treprostinil diethanolamine salt recited in claims 1 and 9. Pet. 41–42; *see also* Ex. 1004, 6, 13; Ex. 1005, 24, 99 (claim 49); Ex. 1009 ¶ 76.

First, as explained in Part II.B above, the present record does not support the conclusion that claims drawn to "[a] product comprising a compound . . ." can be distinguished from prior art products on the basis of differences in the impurity profiles of those products.

Moreover, as explained in detail in Parts II.A, II.B, and II.D above, we determine that the present record supports the contention that the treprostinil product of Moriarty and Phares is the same as that produced according to the steps recited in claims 1 and 9 of '393 patent.

As discussed in Part II.B, the Walsh Declaration fails to disclose the protocols followed in producing the Moriarty and '393 patent treprostinil samples analyzed, and fails to account for the experimental error in Dr. Walsh's impurity measurements. In addition, the inter-batch variability in the types and amounts of impurities observed in treprostinil prepared according to the '393 patent, and the fact that the treprostinil Dr. Walsh prepared according to Moriarty satisfies the FDA purity specification for treprostinil prepared per the '393 patent, lends further support to the conclusion that no structural or

functional differences exist between treprostinil produced according to Moriarty, and that produced according to the '393 patent.

Similarly, as discussed in Part II.D, the present record supports a finding that the impurity profile of treprostinil diethanolamine salt prepared as described by Moriarty in combination with Phares is the same as that prepared according to the '393 patent. Dr. Winkler's testimony regarding the form and melting point of Phares' treprostinil product (Ex. 1009 ¶¶ 59–60, 62), as well as his testimony regarding the disclosure by Phares of the same synthesis process as described by Moriarty (Ex. 1009 ¶¶ 55–57), is consistent with the conclusion that treprostinil diethanolamine generated by reacting Formula 7 of Moriarty with a base, as disclosed by Phares, to form a salt of Formula 7 would result in a treprostinil diethanolamine salt of at least equal purity to that disclosed in the '393 patent.

Accordingly, given the evidence before us in this record, we conclude that SteadyMed has established adequately for purposes of this decision that the combination of Moriarty and Phares renders obvious the treprostinil diethanolamine salt product recited in claims 1 and 9. Because we determine, on the record before us, and for purposes of institution, that the process steps recited in claims 1 and 9 do not impart structural or functional differences to the claimed treprostinil product and are therefore not limiting, we need not address the parties' contentions concerning the obviousness of the recited process steps.

Conclusion

UTC has not raised any additional arguments with regard to the dependent claims other than those addressed above. We have reviewed SteadyMed's evidence, arguments, and claim charts, and conclude that SteadyMed has sufficiently demonstrated that the dependent claims are also rendered obvious by the combination of Moriarty and Phares. Thus, for the foregoing reasons, we conclude that SteadyMed has shown a reasonable likelihood of prevailing on its assertions that claims 1–5, 7–9, 11–14, and 16–20 are obvious in view of Moriarty and Phares.

F. Obviousness Grounds of Unpatentability Based on Moriarty, Phares, Kawakami, and Eğe

SteadyMed asserts that claims 6, 10, 15, 21, and 22 are unpatentable under § 103(a) as obvious in view of Moriarty, Phares or Kawakami, and Eğe. Pet. 37–52. Although SteadyMed nominally identifies this ground of unpatentability as being over "Moriarty (Ex. 1004) with Phares (Ex. 1005) or Kawakami (Exs. 1006 & 1007) and in further combination with Ege (Ex. 1008)" (Pet. 53 (emphasis omitted), as discussed below, SteadyMed explicitly relies on Kawakami in arguing unpatentability in view of Moriarty, Phares, and Eğe. Accordingly, we understand SteadyMed's stated ground of unpatentability as relying on the combination of Moriarty, Phares, Kawakami, and Eğe. Claims 6, 21, and 22 depend, directly or indirectly, from claim 1, and claims 10 and 15 depend directly from claim 9. In support of its assertion, SteadyMed provides detailed explanations as to how the combination of Moriarty, Eğe, Phares, and Kawakami discloses each claim

limitation (*id*.), and relies upon the Winkler Declaration (Ex. 1009) to support its positions.

UTC contends that Kawakami should not be considered as evidence of unpatentability because the declaration certifying the accuracy of the translation is deficient. Prelim. Resp. 38–39. UTC also asserts that Eğe is merely a generic introductory chemistry text, and irrelevant to the '393 patent. *Id*. at 47. UTC further argues that SteadyMed has not identified a rationale for, or expectation of success in, combining either Moriarty, Phares, and Eğe, or Moriarty, Kawakami, and Eğe. *Id*. In addition, UTC contends that SteadyMed improperly asserts that the cited combination would inherently result in the claimed product. *Id*. at 54.

Kawakami

Kawakami describes "a crystalline dicyclohexylamine salt of a methanoprostacyclin derivative, a manufacturing method thereof, and a purifying method thereof." Ex. 1007, 3. Kawakami discloses obtaining a dicyclohexylamine salt by "mixing a methanoprostacyclin derivative [I] . . . with dicyclohexylamine in an appropriate solvent." Ex. 1007, 5–6. Kawakami explains that "[t]he dicyclohexylamine salt of the methanoprostacyclin derivative [I] thus obtained generally has fairly high purity, and the purity can be further improved by recrystallization as needed with the use of an appropriate solvent." *Id*. at 6.

Kawakami further teaches that "[t]he dicyclohexylamine salt obtained by the present invention can be easily reverted to a free

methanoprostacyclin derivative [I] by conventional methods, and the resulting methanoprostacyclin derivative exhibits excellent crystallinity compared with substances not purified according to the present invention." *Id*.

Eğe

Eğe is an organic chemistry textbook. Ex. 1008, 1. Eğe discloses:

> Carboxylic acids that have low solubility in water, such as benzoic acid, are converted to water-soluble salts by reaction with aqueous base. Protonation of the carboxylate anion by a strong acid regenerates the water-insoluble acid. These properties of carboxylic acids are useful in separating them from reaction mixtures containing neutral and basic compounds.

Id. at 8 (reference omitted).

Compliance with 37 C.F.R. § 42.63(b)

Kawakami is a Japanese patent application. Ex. 1006. SteadyMed submitted an English translation of Kawakami (Ex. 1007), as well as an affidavit certifying that translation (Ex. 1011) with its Petition.

UTC nevertheless contends that Kawakami should not be considered as evidence of unpatentability because the President of the translation service, rather than the individual who prepared the translation, executed the certification affidavit. Prelim. Resp. 38–39. UTC asserts that certification affidavit is objectionable because the affiant lacks personal knowledge of the relevant facts, the accuracy of the

translation cannot be determined, and the translator is shielded from cross-examination. *Id*. at 39.

In view of the record before us, and for purposes of this decision, we decline UTC's invitation to disregard Kawakami. No credible prejudice to UTC has been called to our attention, and none is apparent. An English translation of Kawakami was available to UTC in time to prepare its Preliminary Response.[8] Furthermore, UTC has not identified any error in the translation that would call into question its authenticity. Regarding UTC's contention that the accuracy of the translation cannot be determined absent a certification affidavit from the translator himself, we note that the commission of an independent translation would confirm the veracity of the translation submitted by SteadyMed. We also observe that even if the individual personally responsible for generating the English translation of Kawakami had submitted a certification affidavit, UTC would not have had the opportunity to cross-examine him prior to the submission of its Preliminary Response.

Accordingly, on the record before us, and for purposes of this decision, we decline UTC's request that we disregard Kawakami. We observe, however, that the adequacy of the Kawakami translation and

[8] It does not appear that UTC has served objections on SteadyMed concerning the adequacy of the English translation of Kawakami or the certifying affidavit.

certification affidavit may be subject to further challenge during trial.[9]

Rationale to Combine Prior Art Teachings

Building on the rationale for combining Moriarty and Phares discussed in Part II.E above, SteadyMed contends that a relevant skilled artisan would add further purification steps from Kawakami and Eğe because Kawakami "discloses that the dicyclohexylamine salt of a methanoprostacyclin derivative 'can be easily reverted to the free methanoprostacyclin derivative by *conventional methods*,'" and that the "fairly high purity" of the salt obtained "can be further improved by recrystallization as needed with the use of an appropriate solvent." Pet. 53; *see also* Ex. 1007, 6; Ex. 1009 ¶ 83. Dr. Winkler testifies that, as evidenced by Eğe, a relevant skilled artisan "would understand that one such conventional method for converting the dicyclohexylamine salt of a methanoprostacyclin derivative to the free methanoprostacyclin derivative, or converting the treprostinil diethanolamine salt to treprostinil (*i.e.*, the

[9] Pursuant to 37 C.F.R. § 42.64(b)(1), "[a]ny objection to evidence submitted during a preliminary proceeding must be served within ten business days of the institution of the trial. . . . The objection must identify the grounds for the objection with sufficient particularity to allow correction in the form of supplemental evidence." "The party relying on evidence to which an objection is timely served may respond to the objection by serving supplemental evidence within ten business days of service of the objection." 37 C.F.R. § 42.64(b)(2). Furthermore, "[a] motion to exclude evidence must be filed to preserve any objection. . . . The motion may be filed without prior authorization from the Board." 37 C.F.R. § 42.64(c)

free acid) is by treating the salt with a strong acid such as HCl or H_2SO_4." Ex. 1009 ¶ 84; *see also* Pet. 53–54.

Dr. Winkler elaborates on this rationale for combining the cited references, testifying that a relevant skilled artisan

> would want to form the treprostinil diethanolamine salt, purify it, and then convert it back to its free form (*i.e.*, treprostinil) in order to obtain excellent crystallinity and increased purity. And Ege (Ex. 1008, p. 8) teaches that one such method for obtaining the free form of treprostinil or any carboxylic acid would be by treatment of the carboxylate salt with a strong acid.

Ex. 1009 ¶ 88; *see also* Ex. 1008, 8; Pet. 54.

UTC does not address the combination of Moriarty, Eğe, Phares, and Kawakami. Instead, UTC addresses Moriarty, Eğe, and Phares as one combination, and Moriarty, Eğe, and Kawakami as an alternative combination. Prelim. Resp. 46–47.

As an initial matter, UTC asserts that Eğe is irrelevant to the '393 patent because it does not discuss prostacyclin derivatives or pharmaceutical synthesis. *Id*. at 47. UTC argues that Eğe in fact "would teach away or discourage the use of salt formation for purifying a mixture of compounds that includes other carboxylic-acid containing compounds as impurities." *Id*. at 48.

Regarding the combination of Moriarty, Eğe, and Phares, UTC contends that "even though Phares discloses forming a salt from treprostinil free acid, and

Ege generally discusses that carboxylate salt formation was known in the art, there would have been no motivation or expectation of success in using these teachings on the already-formed free acid disclosed in Moriarty." Prelim. Resp. 50. Pertaining to the combination of Moriarty, Eğe, and Kawakami, UTC asserts that SteadyMed "fails to establish that a [relevant skilled artisan] would reasonably expect the teachings of Kawakami to extend to the products in Moriarty." *Id*. at 52.

UTC also argues that Dr. Winkler's testimony regarding the reasons a relevant skilled artisan would want to form treprostinil diethanolamine salt, and treat it with a strong acid to convert it back to its free form (treprostinil) is improperly conclusory. *Id*. at 50, 52.

On the record before us, and for purposes of this decision, we agree that SteadyMed has sufficiently demonstrated that a relevant skilled artisan would have had reason to include the carboxylate salt formation and regeneration of the neutral carboxylic acid with the syntheses of Moriarty and Phares based on the teachings of Kawakami and Eğe.

We recognize, but do not find persuasive, UTC's position that Eğe is irrelevant to the synthesis of prostacyclin derivatives, and that it teaches away from the use of salt formation for purifying a mixture of compounds that includes other carboxylic-acid containing compounds as impurities. First, we observe that SteadyMed relies on Eğe not for any teachings specific to prostacyclin derivative synthesis, but rather, to support the contention that the addition of a strong acid to a carboxylate salt to regenerate the neutral

carboxylic acid is a conventional purification technique in organic chemistry. Pet. 53–55; Ex. 1009 ¶¶ 86, 88. In particular, Dr. Winkler testifies that the "addition of a strong acid to a carboxylate salt to regenerate the neutral carboxylic acid is a common reaction in organic chemistry and this process is well within the skill of one of ordinary skill in the art (indeed, a process that I teach to my organic chemistry students)" (Ex. 1009 ¶ 85), and that Eğe, an introductory organic chemistry text, "discloses that sodium benzoate (i.e., a carboxylate salt) can be converted back to benzoic acid (i.e., a carboxylic acid) by treatment with the acid HCl" (*id*. ¶ 86). On this record, we credit Dr. Winkler's testimony, as it is consistent with the prior art.

Second, we note that even crediting UTC's position that the use of salt formation would not be effective for purifying treprostinil from its stereoisomers (Prelim. Resp. 47–48), the present record suggests that it would be effective for removing other impurities (Pet. 53–55; Ex. 1009 ¶¶ 86, 88). Moreover, as explained below, the present record, including Kawakami, indicates that treprostinil diethanolamine salt formation followed by regeneration of treprostinil using a strong acid is an effective purification step. Pet. 53–55; *see also* Ex. 1007, 6; Ex. 1008, 8; Ex. 1009 ¶¶ 82–90.

Additionally, we agree with SteadyMed that a relevant skilled artisan would have had reason to combine Moriarty, Phares, Kawakami, and Eğe. Pet. 53–55; Ex. 1009 ¶¶ 82–90. For example, Dr. Winkler testifies that a relevant skilled artisan would want to include a carboxylate salt formation and regeneration of the neutral carboxylic acid as described by Eğe with the syntheses of Moriarty and Phares because

Kawakami teaches that "'the dicyclohexylamine salt obtained by the present invention can be easily reverted to a free methanoprostacyclin derivative [I] by conventional methods, and the resulting methanoprostacyclin derivative exhibits excellent crystallinity compared with substances not purified according to the present invention.'" Ex. 1009 ¶ 86; *see also* Ex. 1007, 6; Pet. 53–55. Dr. Winkler additionally testifies that a skilled artisan would be motivated to form treprostinil diethanolamine salt, and treat it with a strong acid to "obtain excellent crystallinity and increased purity" of the final treprostinil product (Ex. 1009 ¶ 88), and that a skilled artisan would have a reasonable expectation of success in performing such reaction because it is "a common reaction in organic chemistry and this process is well within the skill of one of ordinary skill in the art" (*id*. ¶ 90).

On this record, we credit Dr. Winkler's testimony, as it is consistent with the prior art. Moreover, we disagree with UTC that Dr. Winkler's testimony is improperly conclusory. Rather, as illustrated by the excerpts of his testimony referenced above, Dr. Winkler supports his opinions with reference to the cited art, as well as his experience as a chemist and chemistry professor.

Accordingly, on the record before us, we agree that SteadyMed has sufficiently demonstrated that one of ordinary skill in the art would have included the carboxylate salt formation and regeneration of the neutral carboxylic acid of Eğe with the syntheses of Moriarty and Phares based on Kawakami's disclosure that the conversion of salts of prostacyclin derivatives to their free forms by conventional methods increases

purity of the final product. *See KSR*, 550 U.S. at 417 ("[I]f a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill.").

Claims 6, 15, and 21

Claims 6, 15, and 21 each recite the product of either claim 1 or claim 9, subject to additional process steps. For example, claim 6 recites "[t]he product of claim 1, wherein the acid in step (d) is HCl or H_2SO_4." Ex. 1001, 19:39–40. Claim 15 similarly recites "[t]he product of claim 9, wherein the acid in step (d) is HCl." *Id*. at 20:59–60. Claim 21 simply recites "[t]he product of claim 1, wherein step (d) is performed." *Id*. at 21:13.

The present record supports SteadyMed's contention that claims 6, 15, and 21 would have been obvious in view of Moriarty, Eğe, Phares, and Kawakami. Pet. 53–56; Ex. 1009 ¶¶ 82–90. For example, Dr. Winkler testifies that

> the combination of Moriarty (Ex. 1004) and Phares (Ex. 1005) (or Kawakami, Exs. 1006 & 1007) and Ege (Ex. 1008) would disclose . . . treprostinil of at least equal purity to that claimed in the '393 Patent, since the combination of these references discloses the same product and same process of Claims 1 and 9.

Ex. 1009 ¶ 89; *see also* Pet. 54. In addition, as explained above, Dr. Winkler testifies that a skilled artisan would have made the cited combination, with an expectation of success, in order to obtain a

treprostinil product of improved purity. Ex. 1009 ¶¶ 88–90; Pet. 54–55. On this record, we credit Dr. Winkler's testimony.

UTC does not offer evidence or argument to suggest that the additional process steps recited in claims 6, 15, and 21 impart structural or functional differences to the claimed product beyond that discussed above in Parts II.B, II.D, and II.E. Rather, UTC contends that SteadyMed has not asserted that the products of claims 6, 15, and 21 would have been obvious in view of the cited art. Prelim. Resp. 54. UTC frames SteadyMed's position as an argument that the recited process steps would have been obvious, and would have inherently resulted in the claimed product. *Id*.

We do not find UTC's contentions persuasive. We observe that claims 6, 15, and 21 differ from their respective independent claims only in that they require the performance of optional step (d) from claims 1 and 9, and in the case of claims 6 and 15, specify the acid to be used in carrying out that process step. Ex. 1001, 19:39–40, 20:59–60. As set forth in detail in Parts II.A, II.B, II.D, and II.E, on the record before us, and for purposes of this decision, we conclude that the process steps recited in the challenged claims, including step (d), do not impart structural or functional differences over prior art treprostinil products.

Furthermore, we disagree with UTC's characterization of SteadyMed's obviousness argument. We note, for example, that under the general rule for the interpretation of product-by-process claims, which we determine applies here, the products of claims 1, 6, and 21 are interpreted to be the same, namely, the

product of claim 1. Likewise, the same analysis applies for the products of claims 9 and 15.

Accordingly, given the evidence before us in this record, we conclude that SteadyMed has established adequately for purposes of this decision that the combination of Eğe, Phares, and Kawakami renders obvious the treprostinil products of claims 6, 15, and 21. Because we determine, on the record before us, and for purposes of institution, that the process steps recited in claims 6, 15, and 21 do not impart structural or functional differences to the claimed treprostinil product, we do not address the parties' contentions concerning the obviousness of the recited process steps.

Claim 10

Claim 10 recites "[t]he product of claim 9, wherein the purity of product of step (d) is at least 99.5%." Ex. 1001, 20:47–48. The present record supports SteadyMed's contention that claim 10 is obvious in view of Moriarty, Eğe, Phares, and Kawakami. Pet. 55–56; *see also* Ex. 1009 ¶¶ 82–90. As detailed in Parts II.B, II.D, and II.E, the present record supports SteadyMed's position that Moriarty discloses treprostinil free acid having a purity of 99.7% (Pet. 20; *see also* Ex. 1004, 13; Ex. 1009 ¶ 65), and Phares discloses treprostinil diethanolamine salt of the same form and at least the same purity as that claimed in the '393 patent (Pet. 27–28; Ex. 1005, 88–93; Ex. 1009 ¶¶ 59–62). The present record further supports SteadyMed's contention that even if Dr. Walsh's impurity measurements are credited, the 0.1% difference between the purity of the sample prepared according to Moriarty, and claim 10 is within the expected level experimental error for impurity

measurements, and the degree of inter-batch variability in impurity content is such that Dr. Walsh's results are insufficient to support a conclusion of nonobviousness. Pet. 19–22; *see also* Ex. 1009 ¶¶ 63–71.

UTC does not offer evidence or argument to suggest that the additional process step recited in claim 10 imparts structural or functional differences to the claimed product beyond that discussed above in Parts II.A, II.B, II.D, and II.E. Neither does UTC present any additional argument regarding the recited purity requirement beyond those already addressed above. UTC does reassert its position, discussed with regard to claims 6, 15, and 21, that SteadyMed has not asserted that the product of claim 10 would have been obvious in view of the cited art. Prelim. Resp. 54. For the reasons set forth above, however, we do not find this contention persuasive.

Accordingly, given the evidence before us in this record, we conclude that SteadyMed has established adequately for purposes of this decision that the combination of Eğe, Phares, and Kawakami renders obvious the treprostinil product of claim 10. Because we determine, on the record before us, and for purposes of institution, that the process steps recited in claim 10 do not impart structural or functional differences to the claimed treprostinil product, we do not address the parties' contentions concerning the obviousness of the recited process steps at this time.

Claim 22

Claim 22 recites "[t]he product of claim 21, wherein the product comprises a pharmaceutically acceptable

salt formed from the product of step (d)." Ex. 1001, 21:14–16. The present record supports SteadyMed's contention that claim 22 is obvious in view of Moriarty, Eğe, Phares, and Kawakami. Pet. 56–57; *see also* Ex. 1009 ¶¶ 82–90. As discussed above in Parts II.D and II.E, the present record supports SteadyMed's position that the cited combination renders obvious a pharmaceutically acceptable treprostinil salt.

UTC does not offer evidence or argument to suggest that the additional process step recited in claim 22 imparts structural or functional differences to the claimed product beyond that discussed above in Parts II.A, II.B, II.D, and II.E. Neither does UTC present any additional argument regarding the recited purity requirement beyond those already addressed above. UTC does reassert its position, discussed with regard to claims 6, 15, and 21, that SteadyMed has not asserted that the product of claim 22 would have been obvious in view of the cited art. Prelim. Resp. 54. For the reasons set forth above, however, we do not find this contention persuasive

Accordingly, given the evidence before us in this record, we conclude that SteadyMed has established adequately for purposes of this decision that the combination of Eğe, Phares, and Kawakami renders obvious the treprostinil products of claim 22. Because we determine, on the record before us, and for purposes of institution, that the process steps recited in claims 22 do not impart structural or functional differences to the claimed treprostinil product, we do not address the parties' contentions concerning the obviousness of the recited process steps at this time.

Conclusion

For the foregoing reasons, we conclude that SteadyMed has shown a reasonable likelihood of prevailing on its assertions that claims 6, 10, 15, 21, and 22 are obvious in view of Moriarty, Eğe, Phares, and Kawakami.

G. Secondary Considerations of Non-Obviousness

UTC contends that objective indicia of non-obviousness, such as purported evidence of long-felt but unmet need, unexpected results, commercial success, and copying support the patentability of the challenged claims of the '393 patent. Prelim. Resp. 55–58.

We conclude that the evidence of secondary considerations currently of record is not sufficient, at this point in the proceeding, to support UTC's contention. As an initial matter, we observe that "secondary considerations are better considered in the context of a trial when the ultimate determination of obviousness is made." *Crocs, Inc. v. Polliwalks, Inc.*, Case IPR2014-00424, slip op. 16 (PTAB Aug. 20, 2014) (Paper 8). In addition, we note that UTC's contentions regarding long-felt need and unexpected results are predicated on UTC's claim that treprostinil made according to the process described in the '393 patent has fewer impurities than treprostinil produced by other methods. However, as explained in Parts II.B, II.D, and II.E above, the present record does not support that contention. We also observe that UTC does not offer evidence of a nexus between the claimed invention and its commercial success. For example, UTC does not offer evidence concerning its relative share of the market for treprostinil products, or

demonstrating that its revenues or market share increased after it began manufacturing treprostinil according to the process described in the '393 patent. Finally, we note that the mere existence of litigation concerning the '393 patent alone is insufficient to establish copying. *See Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1325 (Fed. Cir. 2004) ("Not every competing product that arguably fails within the scope of a patent is evidence of copying. Otherwise every infringement suit would automatically confirm the nonobviousness of the patent.").

H. Other Asserted Grounds of Unpatentability

SteadyMed also asserts the following ground of unpatentability:

Claims	Basis	Reference(s)
1–5, 7–9, 11–14, and 16–20	§ 103(a)	Moriarty and Kawakami

In light of the grounds specifically discussed above, on the basis of which we institute review, we exercise our discretion and decline to consider these other grounds asserted in the Petition. *See* 37 C.F.R. § 42.108(a). We observe that SteadyMed presents the above ground of unpatentability and the obviousness of claims 1–5, 7–9, 11–14, and 16–20 in view of Moriarty and Phares, a ground on which we institute review, in the alternative.

III. CONCLUSION

For the foregoing reasons, we determine that the information presented in the Petition establishes that there is a reasonable likelihood that SteadyMed would

prevail in challenging claims 1–22 of the '393 patent. At this juncture, we have not made a final determination with respect to the patentability of the challenged claims, nor with respect to claim construction.

IV. ORDER

For the foregoing reasons, it is

ORDERED that pursuant to 35 U.S.C. § 314(a), an *inter partes* review is hereby instituted for the following grounds of unpatentability:

Claims	Basis	Reference(s)
1–5, 7–9, 11–14, and 16–20	§ 102(b)	Phares
1–5, 7–9, 11–14, and 16–20	§ 103(a)	Moriarty and Phares
6, 10, 15, 21, and 22	§ 103(a)	Moriarty, Phares, Kawakami, and Eğe

FURTHER ORDERED that no other ground of unpatentability asserted in the Petition is authorized for this *inter partes* review; and

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial; the trial will commence on the entry date of this decision.

PETITIONER:

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APPENDIX D

STATUTES

35 U.S.C. § 311 - Inter partes review

(a) IN GENERAL.—
Subject to the provisions of this chapter, a person who is not the owner of a patent may file with the Office a petition to institute an inter partes review of the patent. The Director shall establish, by regulation, fees to be paid by the person requesting the review, in such amounts as the Director determines to be reasonable, considering the aggregate costs of the review.

(b) SCOPE.—
A petitioner in an inter partes review may request to cancel as unpatentable 1 or more claims of a patent only on a ground that could be raised under section 102 or 103 and only on the basis of prior art consisting of patents or printed publications.

(c) FILING DEADLINE.—A petition for inter partes review shall be filed after the later of either—

(1) the date that is 9 months after the grant of a patent; or

(2) if a post-grant review is instituted under chapter 32, the date of the termination of such post-grant review.

35 U.S.C. § 312 - Petitions

(a) REQUIREMENTS OF PETITION.—A petition filed under section 311 may be considered only if—

(1) the petition is accompanied by payment of the fee established by the Director under section 311;

(2) the petition identifies all real parties in interest;

(3) the petition identifies, in writing and with particularity, each claim challenged, the grounds on which the challenge to each claim is based, and the evidence that supports the grounds for the challenge to each claim, including—

(A) copies of patents and printed publications that the petitioner relies upon in support of the petition; and

(B) affidavits or declarations of supporting evidence and opinions, if the petitioner relies on expert opinions;

(4) the petition provides such other information as the Director may require by regulation; and

(5) the petitioner provides copies of any of the documents required under paragraphs (2), (3), and (4) to the patent owner or, if applicable, the designated representative of the patent owner.

(b) PUBLIC AVAILABILITY.—
As soon as practicable after the receipt of a petition under section 311, the Director shall make the petition available to the public.

35 U.S.C. § 313 - Preliminary response to petition

If an inter partes review petition is filed under section 311, the patent owner shall have the right to file a preliminary response to the petition, within a time period set by the Director, that sets forth reasons why no inter partes review should be instituted based upon the failure of the petition to meet any requirement of this chapter.

35 U.S.C. § 314 - Institution of inter partes review

(a) THRESHOLD.—
The Director may not authorize an inter partes review to be instituted unless the Director determines that the information presented in the petition filed under section 311 and any response filed under section 313 shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.

(b) TIMING.—The Director shall determine whether to institute an inter partes review under this chapter pursuant to a petition filed under section 311 within 3 months after—

(1) receiving a preliminary response to the petition under section 313; or

(2) if no such preliminary response is filed, the last date on which such response may be filed.

(c) NOTICE.—
The Director shall notify the petitioner and patent owner, in writing, of the Director's determination under subsection (a), and shall make such notice available to the public as soon as is practicable. Such

notice shall include the date on which the review shall commence.

(d) NO APPEAL.—
The determination by the Director whether to institute an inter partes review under this section shall be final and nonappealable.

35 U.S.C. § 315 - Relation to other proceedings or actions

(a) INFRINGER'S CIVIL ACTION.—

(1) INTER PARTES REVIEW BARRED BY CIVIL ACTION.—
An inter partes review may not be instituted if, before the date on which the petition for such a review is filed, the petitioner or real party in interest filed a civil action challenging the validity of a claim of the patent.

(2) STAY OF CIVIL ACTION.—If the petitioner or real party in interest files a civil action challenging the validity of a claim of the patent on or after the date on which the petitioner files a petition for inter partes review of the patent, that civil action shall be automatically stayed until either—

(A) the patent owner moves the court to lift the stay;

(B) the patent owner files a civil action or counterclaim alleging that the petitioner or real party in interest has infringed the patent; or

(C) the petitioner or real party in interest moves the court to dismiss the civil action.

(3) TREATMENT OF COUNTERCLAIM.—
A counterclaim challenging the validity of a claim of a patent does not constitute a civil action challenging the validity of a claim of a patent for purposes of this subsection.

(b) PATENT OWNER'S ACTION.—
An inter partes review may not be instituted if the petition requesting the proceeding is filed more than 1 year after the date on which the petitioner, real party in interest, or privy of the petitioner is served with a complaint alleging infringement of the patent. The time limitation set forth in the preceding sentence shall not apply to a request for joinder under subsection (c).

(c) JOINDER.—
If the Director institutes an inter partes review, the Director, in his or her discretion, may join as a party to that inter partes review any person who properly files a petition under section 311 that the Director, after receiving a preliminary response under section 313 or the expiration of the time for filing such a response, determines warrants the institution of an inter partes review under section 314.

(d) MULTIPLE PROCEEDINGS.—
Notwithstanding sections 135(a), 251, and 252, and chapter 30, during the pendency of an inter partes review, if another proceeding or matter involving the patent is before the Office, the Director may determine the manner in which the inter partes review or other proceeding or matter may proceed, including providing for stay, transfer, consolidation, or termination of any such matter or proceeding.

(e) ESTOPPEL.—

(1) PROCEEDINGS BEFORE THE OFFICE.— The petitioner in an inter partes review of a claim in a patent under this chapter that results in a final written decision under section 318(a), or the real party in interest or privy of the petitioner, may not request or maintain a proceeding before the Office with respect to that claim on any ground that the petitioner raised or reasonably could have raised during that inter partes review.

(2) CIVIL ACTIONS AND OTHER PROCEEDINGS.— The petitioner in an inter partes review of a claim in a patent under this chapter that results in a final written decision under section 318(a), or the real party in interest or privy of the petitioner, may not assert either in a civil action arising in whole or in part under section 1338 of title 28 or in a proceeding before the International Trade Commission under section 337 of the Tariff Act of 1930 that the claim is invalid on any ground that the petitioner raised or reasonably could have raised during that inter partes review.

35 U.S.C. § 316 - Conduct of inter partes review

(a) REGULATIONS.—The Director shall prescribe regulations—

(1) providing that the file of any proceeding under this chapter shall be made available to the public, except that any petition or document filed with the intent that it be sealed shall, if accompanied by a motion to seal, be treated as sealed pending the outcome of the ruling on the motion;

(2) setting forth the standards for the showing of sufficient grounds to institute a review under section 314(a);

(3) establishing procedures for the submission of supplemental information after the petition is filed;

(4) establishing and governing inter partes review under this chapter and the relationship of such review to other proceedings under this title;

(5) setting forth standards and procedures for discovery of relevant evidence, including that such discovery shall be limited to—

(A) the deposition of witnesses submitting affidavits or declarations; and

(B) what is otherwise necessary in the interest of justice;

(6) prescribing sanctions for abuse of discovery, abuse of process, or any other improper use of the proceeding, such as to harass or to cause unnecessary delay or an unnecessary increase in the cost of the proceeding;

(7) providing for protective orders governing the exchange and submission of confidential information;

(8) providing for the filing by the patent owner of a response to the petition under section 313 after an inter partes review has been instituted, and requiring that the patent owner file with such response, through affidavits or declarations, any additional factual evidence and expert opinions on

which the patent owner relies in support of the response;

(9) setting forth standards and procedures for allowing the patent owner to move to amend the patent under subsection (d) to cancel a challenged claim or propose a reasonable number of substitute claims, and ensuring that any information submitted by the patent owner in support of any amendment entered under subsection (d) is made available to the public as part of the prosecution history of the patent;

(10) providing either party with the right to an oral hearing as part of the proceeding;

(11) requiring that the final determination in an inter partes review be issued not later than 1 year after the date on which the Director notices the institution of a review under this chapter, except that the Director may, for good cause shown, extend the 1-year period by not more than 6 months, and may adjust the time periods in this paragraph in the case of joinder under section 315(c);

(12) setting a time period for requesting joinder under section 315(c); and

(13) providing the petitioner with at least 1 opportunity to file written comments within a time period established by the Director.

(b) CONSIDERATIONS.—
In prescribing regulations under this section, the Director shall consider the effect of any such regulation on the economy, the integrity of the patent system, the efficient administration of the Office, and the ability of

the Office to timely complete proceedings instituted under this chapter.

(c) PATENT TRIAL AND APPEAL BOARD.—
The Patent Trial and Appeal Board shall, in accordance with section 6, conduct each inter partes review instituted under this chapter.

(d) AMENDMENT OF THE PATENT.—

(1) IN GENERAL.—During an inter partes review instituted under this chapter, the patent owner may file 1 motion to amend the patent in 1 or more of the following ways:

(A) Cancel any challenged patent claim.

(B) For each challenged claim, propose a reasonable number of substitute claims.

(2) ADDITIONAL MOTIONS.—
Additional motions to amend may be permitted upon the joint request of the petitioner and the patent owner to materially advance the settlement of a proceeding under section 317, or as permitted by regulations prescribed by the Director.

(3) SCOPE OF CLAIMS.—
An amendment under this subsection may not enlarge the scope of the claims of the patent or introduce new matter.

(e) EVIDENTIARY STANDARDS.—
In an inter partes review instituted under this chapter, the petitioner shall have the burden of proving a proposition of unpatentability by a preponderance of the evidence.

35 U.S.C. § 317 - Settlement

(a) IN GENERAL.—
An inter partes review instituted under this chapter shall be terminated with respect to any petitioner upon the joint request of the petitioner and the patent owner, unless the Office has decided the merits of the proceeding before the request for termination is filed. If the inter partes review is terminated with respect to a petitioner under this section, no estoppel under section 315(e) shall attach to the petitioner, or to the real party in interest or privy of the petitioner, on the basis of that petitioner's institution of that inter partes review. If no petitioner remains in the inter partes review, the Office may terminate the review or proceed to a final written decision under section 318(a).

(b) AGREEMENTS IN WRITING.—
Any agreement or understanding between the patent owner and a petitioner, including any collateral agreements referred to in such agreement or understanding, made in connection with, or in contemplation of, the termination of an inter partes review under this section shall be in writing and a true copy of such agreement or understanding shall be filed in the Office before the termination of the inter partes review as between the parties. At the request of a party to the proceeding, the agreement or understanding shall be treated as business confidential information, shall be kept separate from the file of the involved patents, and shall be made available only to Federal Government agencies on written request, or to any person on a showing of good cause.

35 U.S.C. § 318 - Decision of the Board

(a) FINAL WRITTEN DECISION.—
If an inter partes review is instituted and not dismissed under this chapter, the Patent Trial and Appeal Board shall issue a final written decision with respect to the patentability of any patent claim challenged by the petitioner and any new claim added under section 316(d).

(b) CERTIFICATE.—
If the Patent Trial and Appeal Board issues a final written decision under subsection (a) and the time for appeal has expired or any appeal has terminated, the Director shall issue and publish a certificate canceling any claim of the patent finally determined to be unpatentable, confirming any claim of the patent determined to be patentable, and incorporating in the patent by operation of the certificate any new or amended claim determined to be patentable.

(c) INTERVENING RIGHTS.—
Any proposed amended or new claim determined to be patentable and incorporated into a patent following an inter partes review under this chapter shall have the same effect as that specified in section 252 for reissued patents on the right of any person who made, purchased, or used within the United States, or imported into the United States, anything patented by such proposed amended or new claim, or who made substantial preparation therefor, before the issuance of a certificate under subsection (b).

(d) DATA ON LENGTH OF REVIEW.—
The Office shall make available to the public data describing the length of time between the institution of,

and the issuance of a final written decision under subsection (a) for, each inter partes review.

35 U.S.C. § 319 - Appeal

A party dissatisfied with the final written decision of the Patent Trial and Appeal Board under section 318(a) may appeal the decision pursuant to sections 141 through 144. Any party to the inter partes review shall have the right to be a party to the appeal.

APPENDIX E

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Case IPR Unassigned

[Filed October 1, 2015]

STEADYMED LTD.,	)
	)
Petitioner,	)
	)
v.	)
	)
UNITED THERAPEUTICS CORPORATION	)
	)
Patent Owner.	)
	)

Case IPR Unassigned

Patent No. 8,497,393

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 8,497,393 UNDER 37 C.F.R. § 42.100

Mail Stop "Patent Board"
Patent Trial and Appeal Board
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

TABLE OF CONTENTS

TABLE OF EXHIBITS

EXHIBIT	DESCRIPTION	ABBREVIATION
1001	U.S. Patent No. 8,497,393 to Batra, et al.	'393 Patent
1002 - 1	Prosecution History of U.S. Patent No. 8,242,305 (excerpts)	--
1002 - 2	Prosecution History of U.S. Patent No. 8,497,393	--
1003	U.S. Patent No. 6,765,117 to Moriarty, et al.	'117 Patent
1004	J. Org. Chem. 2004, 1890-1902 by Moriarty, et al.	Moriarty
1005	International Publication No. WO 2005/007081 to Phares, et al.	Phares
1006	Japanese Patent App. No. 56-122328A to Kawakami, et al. (Japanese)	Kawakami
1007	Certified English translation of Japanese Patent App. No. 56-122328A to Kawakami, et al.	Kawakami

EXHIBIT	DESCRIPTION	ABBREVIATION
1008	Ege, S. (1989). *Organic Chemistry Second Edition* (pp. 543-547)	Ege
1009	Declaration of Jeffrey D. Winkler, Ph.D.	Winkler Decl.
1010	*Curriculum Vitae* of Jeffrey D. Winkler, Ph.D.	--
1011	Affidavit of Boris Levine certifying Translation of Japanese Patent App. No. 56-122328A to Kawakami, et al.	--
1012	Wiberg, Kenneth (1960), Laboratory Technique in Organic Chemistry (p. 112)	Wiberg
1013	U.S. Patent No. 6,441,245 to Moriarty, et al.	'245 Patent
1014	Schoffstall, "Microscale and Miniscale Organic Chemistry Laboratory Experiments," 200-202 (2d ed.) (2004)	Schoffstall

EXHIBIT	DESCRIPTION	ABBREVIATION
1015	U.S. Patent No. 3,703,544 to Morozowich, et al.	'544 Patent
1016	U.S. Patent No. 3,888,916 to Sinkula, et al.	'916 Patent
1017	"Getting Started in HPLC," Section 4D: Precision and Accuracy, available at http://www.lcresources.com/resources/getstart/4d01.htm (accessed Sept. 29, 2015)	--
1018	Gilbert, "Experimental Organic Chemistry: A Miniscule and Microscale Approach," 113-117 (5th. ed.) (2011)	Gilbert[1]

SteadyMed Ltd. ("Petitioner") in accordance with 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42.100 *et seq.,* requests that the United States Patent and Trademark

[1] For ease of reference, all citations to the above references are to the bates-labeled page number. Petitioner utilizes the "column, line number" format, however, for any referenced U.S. Patents (*i.e.,* Exhibit Nos. 1001, 1003, 1013, 1015, and 1016).

Office ("USPTO") proceed with an *inter partes* review of Claims 1-22 of U.S. Patent No. 8,497,393 (the '393 Patent") (Ex. 1001).

I. COMPLIANCE WITH FORMAL REQUIREMENTS

A. Mandatory Notices Under 37 C.F.R. § § 42.8(b)(1)-(4)

1. Real Party-in-Interest

SteadyMed Ltd., SteadyMed Therapeutics, Inc., and SteadyMed U.S. Holdings, Inc. are the real parties-in-interest.

2. Related Matters

Petitioner advises that to its knowledge there are no related matters to which it is a party. Petitioner further advises that the '393 Patent is subject to the following U.S. District Court litigations, currently pending in the District of New Jersey: (1) *United Therapeutics Corp. v. Sandoz, Inc*., Civ. No. 14-cv-05499; (2) *United Therapeutics Corp. v. Teva Pharmaceuticals U.S.A., Inc*., Civ. No. 14-cv-05498; and (3) *United Therapeutics Corp. v. Watson Laboratories, Inc*., Civ. No. 15-cv-05723.

3. Lead And Back-Up Counsel

Pursuant to 37 C.F.R. § 42.8(b)(3) and 42.10(a), Petitioner provides the following designation of counsel: Lead counsel is Stuart E. Pollack (Reg. No. 43,862) and backup counsel is Lisa A. Haile (Reg. No. 38,347), both at email address: Steadymed-IPR@dlapiper.com. Postal and hand delivery for both is DLA Piper LLP (US), 1251 Avenue of the Americas,

27th Floor, New York, New York 10020. Telephone for Dr. Pollack is (212) 335-4964; telephone for Dr. Haile is (858) 677-1456. The fax for both is (212) 335-8464.

4. Powers of Attorney and Service Information

Pursuant to 37 C.F.R. § 42.10(b), a Power of Attorney accompanies this Petition. Petitioner consents to service by email at Steadymed-IPR@dlapiper.com.

B. Proof of Service on the Patent Owner

As identified in the attached Certificate of Service, a copy of this Petition in its entirety is being served to Patent Owner ("Patentee") at the address listed in the USPTO's records by overnight courier pursuant to 37 C.F.R. § 42.6.

C. Fees

A fee of $26,200 has been paid for this Petition. Twenty-two (22) claims are being reviewed. The undersigned further authorizes the United States Patent and Trademark Office, including the Patent Trial and Appeal Board to charge any additional fee that might be due or required to Deposit Account No. 07-1896.

II. GROUNDS FOR STANDING

In accordance with 37 C.F.R. § 42.104(a), Petitioner certifies that the '393 Patent is available for *inter partes* review and that Petitioner is not barred or estopped from requesting an *inter partes* review challenging the patent claims on the grounds identified in this Petition.

III. STATEMENT OF PRECISE RELIEF REQUESTED

In accordance with 37 C.F.R. § 42.22, Petitioner respectfully requests that Claims 1-22 of the '393 Patent be found invalid for the reasons set forth below.

IV. IDENTIFICATION OF CHALLENGE

Inter partes review is requested in view of the following references:

- **Exhibit 1004**: J. Org. Chem. 2004, 1890-1902 by Moriarty, et al. ("Moriarty");
- **Exhibit 1005**: International Publication No. WO 2005/007081 to Phares, et al. ("Phares");
- **Exhibit 1006** (Japanese) and **Exhibit 1007** (English): Japanese Patent App. No. 56-122328A to Kawakami, et al. ("Kawakami");
- **Exhibit 1008**: *Organic Chemistry Second Edition* (pp. 543-547) by Ege ("Ege").

Pursuant to 37 C.F.R. § 42.63(b), Exhibit 1011 contains an affidavit attesting that a professional translator and interpreter fluent in the English and Japanese languages translated Kawakami (Ex. 1006).

Each of the patents and printed publications set forth below is prior art to the '393 Patent:

Ground	Proposed Statutory Rejections for the '393 Patent
1	Claims 1-5, 7-9, 11-14 and 16-20 are anticipated by Phares (Ex. 1005) pursuant to 35 U.S.C. §102(b).
2	Claims 1-5, 7-9, 11-14 and 16-20 are rendered obvious by a combination of Moriarty (Ex. 1004) in view of either Phares (Ex. 1005) or Kawakami (Exs. 1006 & 1007) pursuant to 35 U.S.C. §103.
3	Claims 6, 10, 15, 21 and 22 are rendered obvious by a combination of Moriarty (Ex. 1004) in view of either Phares (Ex. 1005) or Kawakami (Exs. 1006 & 1007) and further in view of Ege (Ex. 1008) pursuant to 35 U.S.C. §103.

Petitioner also relies on the Declaration of Jeffrey D. Winkler, Ph.D. (Ex. 1009) in further support of its arguments.

V. LEVEL OF ORDINARY SKILL IN THE ART

A person of ordinary skill in the area of chemistry at the time of the alleged invention would have a master's degree or a Ph.D. in medicinal or organic chemistry, or a closely related field. (Ex. 1009, Winkler Decl., ¶ 14). Alternatively, a person of ordinary skill would include an individual with a bachelor's degree and at least five years of practical experience in medicinal or organic chemistry. (*Id*., at ¶ 14).

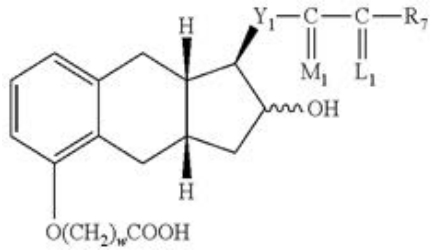
VI. SUMMARY OF THE '393 PATENT

A. Brief Description of the '393 Patent

The '393 Patent is entitled "Process to Prepare Treprostinil, The Active Ingredient in Remodulin™." The claims of the '393 Patent are product-by-process claims. These claims include two independent (Claims 1 and 9) and twenty dependent claims.

The '393 Patent discloses an "improved process" to prepare prostacyclin derivatives such as treprostinil. (Ex. 1001, Abstract). Claim 1 is drawn to a product comprising a compound of a genus that includes the treprostinil compound, or a pharmaceutically acceptable salt thereof. Claim 9 is identical to Claim 1 except that it is drawn to a product comprising the specific treprostinil compound, a species of the genus of Claim 1, made by the same process.

Each of the independent claims includes limitations that the claimed compound is made by a process comprising three specified steps and one optional step: (a) alkylating a prostacyclin derivative (*e.g.*, a benzindene triol precursor to treprostinil acid) to form an alkylated prostacyclin derivative (*e.g.*, a benzindene nitrile precursor to treprostinil acid); (b) hydrolyzing the alkylated prostacyclin derivative with a base to form a prostacyclin acid (*e.g.*, treprostinil acid); (c) contacting the prostacyclin acid (*e.g.*, treprostinil acid) with a base to form a prostacyclin carboxylate salt (*e.g.*, a treprostinil salt); and (d) optionally reacting the prostacyclin carboxylate salt (*e.g.*, a treprostinil salt) formed in step (c) with an acid to form a compound or a pharmaceutically acceptable salt of:



(Ex. 1001).

The alkylating and hydrolyzing steps in the synthesis of treprostinil and the other claimed compounds, as set forth in steps (a) – (b) of Claims 1 and 9, were fully disclosed in prior art to the '393 Patent, including U.S. Patent No. 6,765,117 (the '117 Patent) (Ex. 1003), and in Moriarty et al., J. Org. Chem., 1890-1902 (2004) (Ex. 1004, referred to as "Moriarty"), as well as other publications. Patent Owner admits that steps (a) ("alkylating") and (b) ("hydrolyzing") were in the prior art. (*See* Prosecution History (Ex. 1002-1), p. 109; '393 Patent, (Ex. 1001), col. 1, lines 22-28 (incorporating Moriarty (Ex. 1004), the '117 Patent (Ex. 1003), and U.S. Patent No. 6,441,245 (Ex. 1013) by reference, and col.7, lines 17-20 (describing '245 Patent's process as the same as in '393 Patent)).

The '393 Patent addresses an alleged "improvement" to Moriarty through the addition of steps (c) and optionally (d), which claim a standard, basic organic chemistry purification by a precipitation technique: converting a free carboxylic acid into a salt using a weak base and then precipitating it to remove potential impurities, and then, optionally converting the salt back to the free acid. (*See, e.g.,* Ex. 1001, col.

17, lines 27-40) (describing the benefits of the disclosed processes as providing a "better quality" final product that removes impurities). These precipitation procedures were well-known in the art – indeed, they are no more than basic organic chemistry techniques and standard chemical purification – and they were fully disclosed in numerous prior art references, including basic organic chemistry textbooks. Additionally, as discussed in greater detail below and in the accompanying Declaration of Jeffrey D. Winkler (Ex. 1009), the claimed '393 Patent process does not produce a product that is materially distinct from the product produced by the prior art.

B. Summary of the Prosecution History of the '393 Patent

The '393 Patent issued July 30, 2013 from application No. 13/548,446, filed July 13, 2012. Application No. 13/548,446 is a continuation of application No. 12/334,731, filed on December 15, 2008, now U.S. Patent No. 8,242,305. Both patents claim priority to provisional application No. 61/014,232, filed December 17, 2007.

During prosecution, the Examiner rejected the pending claims (substantially identical to issued Claims 1-22 of the '393 Patent) under 35 U.S.C. §102(b) as being anticipated by Moriarty (Ex. 1004; *see also* Ex. 1002-2, p. 295, 1/3/2013 Office Action; pp. 327-329, 5/15/2013 Office Action). As noted above, Moriarty discloses the synthesis for treprostinil, which involves, *inter alia*, the isolation of treprostinil prior to the formation of treprostinil salt. The Examiner stated that Moriarty discloses a compound having the same structure of the claimed product disclosed in the '393

Patent. (Ex. 1002-2, p. 295, 1/3/2013 Office Action; pp. 327-329, 5/15/2013 Office Action). The Examiner further stated that the claims are product-by-process claims, and since the product disclosed in the prior art is the same as the claimed product, the "patentability of the product does not depend on the method of its production." (*Id*.).

In response, Patent Owner submitted arguments and a Declaration under 37 C.F.R. §1.132 by Dr. David Walsh, one of the inventors, and Executive Vice President of Chemical Research and Development at United Therapeutics Corporation (the "Walsh Declaration") (Ex. 1002, pp. 346-350, Walsh Declaration). The Walsh Declaration provides data from "representative Certificates of Analysis" with impurity profiles for treprostinil free acid prepared according to the process of Moriarty (Ex. 1004), and treprostinil diethanolamine and treprostinil free acid prepared according to the process of the '393 Patent. (*Id*.). Relying on the Walsh Declaration, Patent Owner differentiated its synthesis of treprostinil by emphasizing that its product (treprostinil) was different than the product of Moriarty (Ex. 1002-2, pp. 343-344, 6/5/2013 Remarks; pp. 346-350, Walsh Declaration) because: (1) the product of Moriarty is "physically different" than the instant claims, as a "base addition salt is formed *in situ* with treprostinil that has not been previously isolated"; and (2) the product of Moriarty contained more impurities:

> "In the response filed February 8, 2013, Applicants submitted that the product of Moriarty 2004 is physically different from the product of claims 1 and 10, in which a base

> addition salt is formed in situ with treprostinil that has not been previously isolated. Specifically, Applicants noted that when a batch of treprostinil acid made by the type of process disclosed in Moriarty 2004 was analyzed by the applicants, it was found to contain small amounts of 4 different impurities (benzindene triol, treprostinil methyl ester, and 2 different stereoisomers of treprostinil) […] Applicants explained that this physical difference in the product resulted directly from the steps recited in claims 1 and 10, in which a salt is formed in situ without previously isolating treprostinil."

(Ex. 1002-2, pp. 343-344). The Walsh Declaration demonstrated a treprostinil purity of 99.8%, above both Claim 2 and Claim 10's 99.5% purity level and Moriarty's 99.7% purity level, and according to Dr. Walsh, Moriarty's purity is really 99.4%, and not 99.7% as Moriarty reported. (Ex. 1002-2, pp. 347). These alleged purity differences were intended to rebut the Examiner's statement that "[o]n page 1902 [of Moriarty] … [i]n the second column 99.7 pure compound 7 [treprostinil] is disclosed thereby meeting the purity limitations of claims 2 and 11." (Ex. 1002-2, pp. 327-328). In fact, these purity differences are illusory, and reflect differences in unclaimed process conditions and the precision of the HPLC instrument measuring impurities, and cannot confer patentability.

VII. CLAIM CONSTRUCTION

A claim subject to *inter partes* review receives the "broadest reasonable construction in light of the specification of the patent in which it appears." 42 C.F.R. § 42.100(b). This means that the words of the

claim are given their plain meaning from the perspective of one of ordinary skill in the art unless that meaning is inconsistent with the specification. *In re Zletz*, 893 F.2d 319, 321 (Fed. Cir. 1989). Indeed, there is a "heavy presumption" that a claim term carries its ordinary and customary meaning. *CCS Fitness, Inc. v. Brunswick Corp*., 288 F.3d 1359, 1366 (Fed. Cir. 2002). Here, each claim term carries its ordinary and customary meaning, with the exception of the following terms that should be construed:

"***Product***": "Product" appears in each independent Claim 1 and 9, and in dependent Claim 22. The broadest reasonable interpretation of "product" is "chemical composition." Both claims use the transition "comprising" ("a product comprising…" and "a process comprising…"), which is expressly defined in the '393 Patent specification: "The expression 'comprising' means 'including but not limited to.' Thus, other non-mentioned substances, additives, carriers, or steps may be present." (Ex. 1001, col. 4, lines 23-24). "Product," is therefore properly defined as a "chemical composition," which includes the treprostinil compound along with other substances (including impurities). A composition connotes more than one element or ingredient; it is a chemical composition because treprostinil is a chemical and a composition containing treprostinil is a chemical composition. For these reasons, "product" should be construed as "a chemical composition."

"***A product comprising a compound of formula I/IV or a pharmaceutically acceptable salt thereof***" (Claims 1 & 9): This term appears in each independent claim, Claims 1 and 9. The broadest reasonable interpretation is "a chemical composition

that includes, but is not limited to, a compound of Formula I, or a pharmaceutically acceptable salt thereof, and that may also include other non-mentioned substances (including impurities), additives, or carriers, without limitation as to the types or relative amounts thereof." Petitioner's proposed construction incorporates Patent Owner's definition of "comprising" in the '393 Patent specification (Ex. 1001, col. 4, lines 23-25). For example, isolating treprostinil during the process is included in the claims, since it is an additional process step allowed by the transitional phrase "comprising."

"***A process comprising***" and "***the process comprising***" (Claims 1 & 9): These terms appear in each independent claim, Claims 1 & 9. The broadest reasonable interpretation is "a process that includes, but is not limited to, the recited process steps, and may include, without limitation, any other non-recited steps." This construction is supported by Patent Owner's definition of "comprising" as meaning "including but not limited to" and that "other non-mentioned…steps may be present." (Ex. 1001, col. 4, lines 23-25). The term "comprising" dictates that while the claimed process must include the recited steps it is not otherwise limited and can include any other non-recited steps.

Because the claim construction standard in this proceeding differs from that used in U.S. district court litigations, Petitioner expressly reserves the right to assert different claim construction positions under the standard applicable in district court for any term of the '393 Patent in any district court litigations, should

Petitioner become a party to any future litigation involving the '393 Patent.

VIII. THERE IS A REASONABLE LIKELIHOOD THAT AT LEAST ONE CLAIM OF THE '393 PATENT IS UNPATENTABLE

A. Identification of the References As Prior Art

Moriarty was published in 2004 in the Journal of Organic Chemistry, Volume 69, No. 6. (Ex. 1004). Moriarty is prior art to the '393 Patent under 35 U.S.C. §103, as a publication under § 102(b).

Phares was published January 27, 2005. (Ex. 1005). Phares is prior art to the '393 Patent under 35 U.S.C. §§102(b) and 103.

Kawakami was published September 25, 1981 to Kawakami, et al. (Exs. 1006 & 1007). Kawakami is prior art to the '393 Patent under 35 U.S.C. §103, as a publication under § 102(b).

Ege was published in 1989 in *Organic Chemistry, Second Edition*, at pages 543-547. (Ex. 1008). Ege is prior art to the '393 Patent under 35 U.S.C. §103, as a publication under § 102(b).

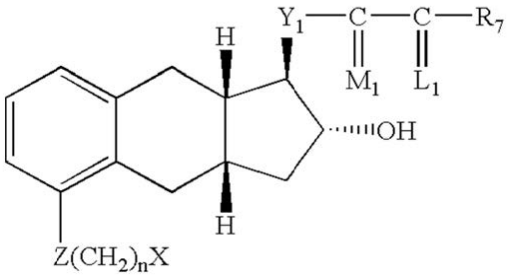
B. State of the Prior Art & Summary of Invalidity Arguments

There are three separate – and strong – bases for invalidation of the '393 Patent: (1) the synthesis of the claimed compounds including treprostinil and treprostinil diethanolamine salt was well-known in the art; (2) the '393 Patent's only alleged "improvement" over the prior art involves nothing more than basic

organic chemistry 101 – standard chemical purification through salt formation and precipitation, and this salt formation and purification step was carried out on treprostinil in the prior art; and (3) since the claims of the '393 Patent are product-by-process claims and the claimed process does not produce a product that is materially distinct from the product produced by the prior art, the claims of the '393 Patent are invalid as anticipated and obvious. Accordingly, all claims of the '393 Patent should be held invalid, as discussed in further detail below.

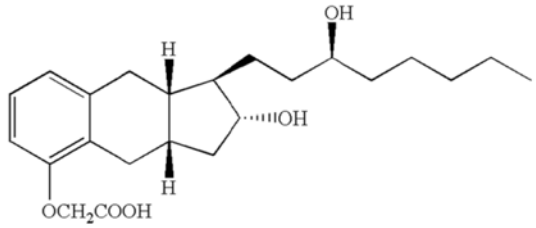
1. *Steps (a) – (b): The Synthesis of Treprostinil Was Well-Known*

Before December 17, 2007, syntheses for numerous prostacyclin derivatives, such as treprostinil, and intermediate compounds useful in their syntheses were well-known. These prostacyclin derivatives and intermediates include the following general structures:

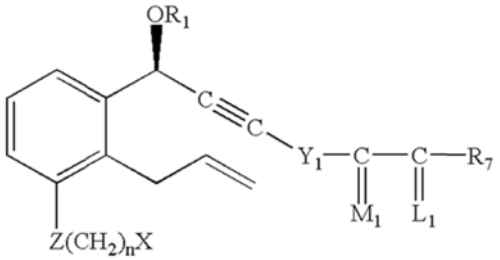


(*see e.g.,* the '117 Patent, Ex. 1003, Claim 1). For example, the '117 Patent (Ex. 1003) includes the synthesis of treprostinil (which is the case in which, Z is O, n is 1, X is COOH, Y_1 is CH_2CH_2-, M_1 is a H and a OH group in the S configuration (*i.e.,* the same stereoisomer configuration found in the structure of

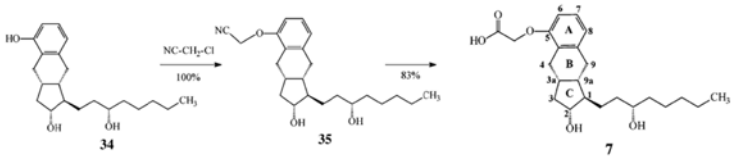
treprostinil (below)), L_1 is α-H; β-H, and R_7 is -$(CH_2)_3$-CH_3) amongst its many examples. In addition, both Moriarty (Ex. 1004) and Phares (Ex. 1005) further disclose syntheses of treprostinil. For example, Claim 3 of the '117 Patent (Ex. 1003) discloses the structure of treprostinil (below),



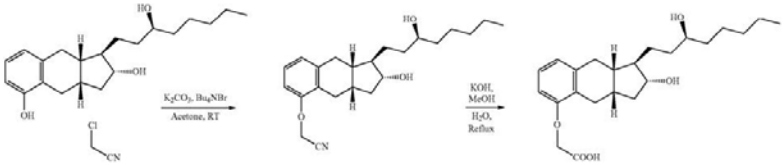
which is produced by a process for making 9-deoxy-PGF1-type compounds, the process comprising cyclizing the following starting compound:



As noted above, steps (a) – (b) of Claims 1 and 9 of the '393 Patent disclose the synthesis of prostacyclin derivative acids that include treprostinil acid, which is also disclosed in Moriarty (Ex. 1004) and the '117 Patent (Ex. 1003). For example, Moriarty (Ex. 1004) at p. 6 and p. 3 discloses the following synthetic scheme for making treprostinil acid:



And the ’393 Patent (Ex. 1001) at cols. 9-10 discloses the same synthetic scheme for making treprostinil acid:



Accordingly, the only alleged “improvement” to Moriarty in the ’393 Patent was the addition of step (c) and **optionally** step (d) of Claims 1 and 9.

2. *Steps (c) & (d): Formation of a Carboxylate Salt from a Carboxylic Acid and the Addition of an Acid to a Carboxylate Salt to Regenerate the Carboxylic Acid is Standard Chemical Purification Known in the Art*

Steps (c) and (d) of Claims 1 and 9 disclose nothing more than basic organic chemistry techniques for purification of a carboxylic acid, such as treprostinil acid, well described in the prior art years before December 17, 2007. The formation of a carboxylate salt, by the addition of a weak base to a neutral carboxylic acid, and the subsequent addition of a strong acid to regenerate carboxylic acid, as disclosed in steps (c) and (d), is standard chemistry purification – *i.e.*, organic chemistry 101. Indeed, similar general

purification techniques were described in numerous textbooks and literature, such as basic introductory organic chemistry textbooks, well before the December 17, 2007 priority date for the '393 Patent. For example, Wiberg (Ex. 1012), an organic chemistry lab textbook (Ex. 1012) provided to organic chemistry students, explicitly states:

> A typical example is the purification of a water-insoluble solid carboxylic acid by dissolving it in sodium hydroxide solution, filtering, precipitating the compound by the addition of acid. A similar procedure may be used with amines: dissolve the compound in acid and precipitate it with a base. These procedures usually work quite well in that they utilize a chemical reaction to aid in separation from nonacidic or nonbasic impurities.

(Ex. 1012, p. 6; *see also* Ex. 1009, Winkler Decl., ¶ 42). Similarly, Schoffstall (Ex. 1013), describes an experiment in which carboxylic acid is separated from neutral and basic organic compounds by conversion to a salt. Addition of an acid, such as HCl, then regenerates the carboxylic acid, which can then be filtered or extracted into an organic solvent. (Ex. 1013, pp. 3-40; *see also* Winkler Decl., ¶ 42). As the '393 Patent claims do not require isolation (or non-isolation) of the claimed treprostinil prior to formation of the treprostinil diethanolamine salt, general purification procedures, as disclosed in basic organic chemistry textbooks like Wiberg or Schoffstall, accordingly fall within the '393 Patent claims. *See also* (Ex. 1002-2, p. 343, 2/8/2013 Remarks ("…the steps recited in claims

1 and 10, in which a salt is formed *in situ* without previously isolating treprostinil").

More specifically, contacting a carboxylic acid of a prostacyclin derivative, such as treprostinil, with a base to form a salt, followed by the addition of a strong acid to regenerate the carboxylic acid, was a well-known chemical purification technique in the prior art. For example:

- ***Kawakami*** (Ex. 1007), entitled "Crystalline Amine Salt of Methanoprostacyclin Derivative, Manufacturing Method thereof, and **Purifying Method** thereof" (bolding added), is directed to the preparation and use of dicyclohexylamine (*i.e.*, a base) to form a crystalline dicyclohexylamine salt of a methanoprostacyclin derivative, in order to purify the methanoprostacyclin. Kawakami further discloses that the dicyclohexylamine salt of a methanoprostacyclin derivative can be easily reverted to the free methanoprostacyclin derivative by conventional methods (Ex. 1007, p. 6), such as treating the salt with a strong acid such as HCl or H_2SO_4. Per Kawakami, the salt that is obtained has "fairly high purity and the purity can be further improved by recrystallization as needed with the use of an appropriate solvent." (*Id.*).

- ***Phares*** (Ex. 1005), entitled "Compounds and Methods for Delivery of Prostacyclin Analogs," discloses that the preparation of treprostinil diethanolamine includes the step of adding and dissolving diethanolamine (*i.e.*, a base) to treprostinil that is dissolved in a 1:1 molar ratio mixture of ethanol: water. (Ex. 1005, p. 24, bottom para.). This treprostinil diethanolamine can be

further precipitated and purified to form the purer and more stable crystal form called "Form B." (Ex. 1005, pp. 85-93).

- ***Ege*** (Ex. 1008), an organic chemistry textbook, discloses that sodium benzoate (*i.e*., a carboxylate salt) can be converted back to benzoic acid (*i.e*., a carboxylic acid) by treatment with the acid HCl. (Ex. 1008, p. 8).

3. *The Claimed Treprostinil and Treprostinil Diethanolamine Salt is Not Distinct from the Prior Art*

As noted above and as recognized by the Patent Office during prosecution, the '393 Patent claims are product-by-process claims. The process limitations are not accorded any weight for determining the validity of the claims of the '393 Patent. *See, e.g., Amgen Inc. v. F. Hoffman-La Roche Ltd*., 580 F.3d 1340, 1369 (Fed. Cir. 2009) ("In determining validity of a product-by-process claim, the focus is on the product and not the process of making it"); *see also* MPEP § 2113 (citing *In re Thorpe*, 777 F.2d 695, 698 (Fed. Cir. 1985)). The process in a product-by-process claim merits weight in reviewing the prior art only if it imparts some unique and novel property or structure in the resulting product. Such is not the case here. As noted during prosecution, Patent Owner differentiated its synthesis of treprostinil from Moriarty (Ex. 1004) by emphasizing that its product (treprostinil) contained less impurities than the product of Moriarty. Accordingly, there are three reasons why the claimed treprostinil is not distinct from the same compound in the prior art:

(1) First, during prosecution, Patent Owner provided a declaration claiming to show that its

purification method achieved 99.8% purity (Ex. 1002-2, p. 348) despite the admission in the '393 Patent itself that: "In one embodiment, the purity of compound of formula IV is at least 90.0%, 95.0%, 99.0%, 99.5%," ('393 Patent, Ex. 1001, col. 8, lines 66-67)[2] where the compound of Formula IV is treprostinil. This admission shows that the purity of treprostinil may be as low as 90.0%, and Patent Owner's suggestion that 99.8% is achieved or that greater than 99.5% is always achieved is based on a particular set of process steps that are not claimed and which must have been found after the filing date.

(2) Second, Patent Owner's claimed 99.5% purity, which Patent Owner's Walsh Declaration contends was unique (Ex. 1002-2, p. 347), and which is claimed in dependent Claims 2 and 10, is actually 0.2% ***less*** than the 99.7% purity measured by Moriarty in the prior art (*e.g.*, Ex. 1004, Moriarty, p. 13). As the synthesis of treprostinil was well-known in the art at the time of the alleged invention, a mere difference in degree of purity, such as 0.2%, is an insufficient bases for patentability and provides no material difference from the prior art. *See Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013) ("Results which differ by percentages are differences in degree rather than kind, where the modification of the percentage is within the capabilities of one skilled in the art at the time."). Additionally, inventor David Walsh, who provided a declaration contending that Moriarty produced an impurity level of 99.4% (Ex. 1002-2, p. 347), contrary to Moriarty's own 99.7% measurement,

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[2] *See also* '393 Patent col.7, lines 14-15.

did not explain what process conditions contributed to the specific impurity levels he measured, and why his measurement differed from what Moriarty reported. (Ex. 1009, Winkler Decl., ¶¶ 65, 67). Indeed, the data in the Walsh Declaration was derived from a limited sample, which could result in significant batch-to-batch variations in the impurity profile of each batch of treprostinil. (Ex. 1009, Winkler Decl., ¶ 66).

(3) And, third, the difference between the 99.4% measured by Moriarty, and 99.5% claimed in the '393 Patent, *i.e.*, 0.1%, is a percentage that is well within experimental error for measuring impurities, as Dr. Winkler explains. (Ex. 1009, Winkler Decl., ¶¶ 68-70). Indeed, the '393 Patent itself discloses a purity of the claimed compound of 100.4% (Ex. 1001, col. 13, line 64), indicating, as Dr. Winkler notes, that the deviation for the instrument the inventors themselves were using was about ± 0.4%, far greater than the 0.1% difference, and comparable to the difference between 99.8% and 99.4% Dr. Walsh measured between alleged "'393 product" and Moriarty's product as measured by Dr. Walsh. (Ex. 1009, Winkler Decl., ¶ 70-71). Indeed, expected instrumental deviations and expected precision of this equipment would explain the 0.3% difference between Moriarty's reported 99.7% value and Dr. Walsh's 99.4% value.

Accordingly, and as discussed in further detail below, since the synthesis of treprostinil, its subsequent purification steps involving reaction with a base such as diethanolamine to form a salt, and the optional reaction of an acid with the salt to regenerate the acid, were already well-known to those of skill in the art as noted in numerous prior art references, and

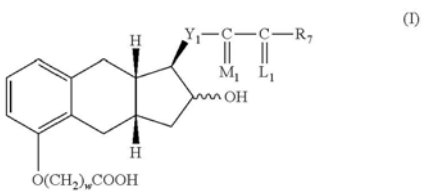
the claimed treprostinil is not distinct from the same compound in the prior art, the '393 Patent (Ex. 1001) should be held invalid.

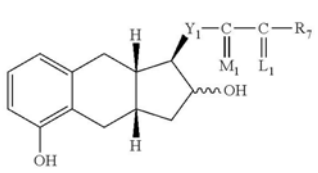
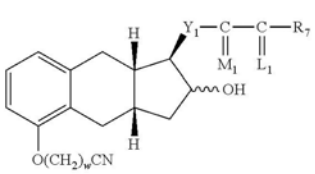
IX. CLAIM-BY-CLAIM EXPLANATION OF GROUNDS FOR UNPATENTABILITY

A. Ground 1: Detailed Explanation Under 37 C.F.R. § 42.104(b) of How Phares (Ex. 1005) Anticipates Claims 1-5, 7-9, 11-14 and 16-20 Under 35 U.S.C. § 102(b).

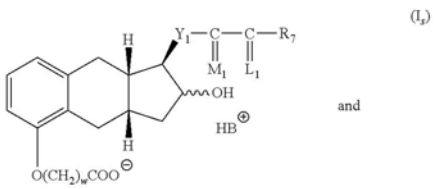
Phares (Ex. 1005) is §102(b) prior art to the '393 Patent. Phares anticipates Claims 1-5, 7-9, 11-14, and 16-20 as set forth in further detail below.

Claim 1

'393 Patent Claim Element	**Disclosure in Phares (Ex. 1005)**
1. (pre) A product comprising a compound of formula I  (I) or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising	Ex. 1005, pp. 41-42 (w is 1, Y_1 is CH_2CH_2-, M_1 is a H and a OH group in the S configuration; α-H, L_1 is α-H; β-H, and R_7 is $–(CH_2)_3$-CH_3 in an enantiomer of Formula 2); pp. 85-93 (using treprostinil diethanolamine salt in clinical trials as a pharmaceutically acceptable salt); p. 99, Claim 49.
1. (a) alkylating a compound of structure II with an	Ex. 1005, pp. 41-42.

alkylating agent to produce a compound of formula III,  (II)  (III) wherein w=1, 2, or 3; Y_1 is trans-CH=CH—, cis-CH=CH—, —$CH_2(CH_2)_m$—, or —C≡C—; m is 1, 2, or 3; R_7 is (1) —C_pH_{2p}—CH_3, wherein p is an integer from 1 to 5, inclusive, (2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl,	

being the same or different, (3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl,(4) cis-$CH{=}CH{-}CH_2{-}CH_3$, (5) $-(CH_2)_2-CH(OH)-CH_3$, or (6) $-(CH_2)_3-CH{=}C(CH_3)_2$; $-C(L_1)-R_7$ taken together is (1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_5)alkyl;(2) 2-(2-furyl)ethyl, (3) 2-(3-thienyl)ethoxy, or (4) 3-thienyloxymethyl; M_1 is α-OH:β-R_5 or α-R_5β-OH or α-OR_1:β-R_5 or α-R_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group, and L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is	

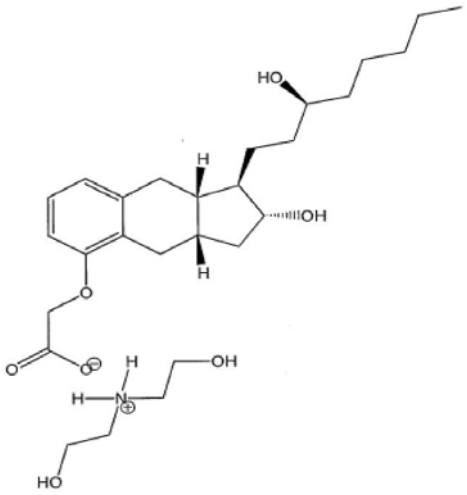
hydrogen or fluoro,	
1. (b) hydrolyzing the product of formula III of step (a) with a base,	Ex. 1005, pp. 41-42.
1. (c) contacting the product of step (h) [*sic*] with a base B to form a salt of formula I_s. 	Ex. 1005, p. 24; pp. 85-93; p. 99, Claim 49.
1. (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula I.	No disclosure needed as this step is optional.

Phares inherently discloses the same synthesis of treprostinil as set forth in Claim 1 of the '393 Patent in the case where w is 1, Y_1 is CH_2CH_2-, M_1 is a H and a OH group in the S configuration; L_1 is α-H; β-H, and R_7 is $–(CH_2)_3$-CH_3. (Ex. 1005, at pp. 41-42; Ex. 1009, Winkler Decl., ¶ 48). Phares discloses the same treprostinil diethanolamine salt (Ex. 1005, p. 24; p. 99, Claim 49) as the '393 Patent (Ex. 1009, Winkler Decl., ¶¶ 50-53), and further discloses use of the treprostinil diethanolamine salt in the same "polymorph" (crystal form) – Form B – as the '393 Patent. (Ex. 1001, col. 12, lines 34-51; Ex. 1005, pp. 90-91; Winkler Decl., ¶ 58). This salt is made by exactly the same process step as in Claim 1(c): by contacting the product of step (b) with diethanolamine base to form the salt whose structure

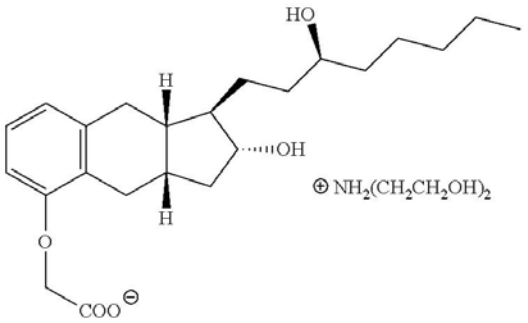
is displayed in Phares Claim 49 (Ex. 1005, p. 99). This shows that Phares necessarily discloses the same process steps to make treprostinil diethanolamine salt claimed in the '393 Patent, and thus inherently anticipates Claim 1 of the '393 Patent. (Ex. 1009, Winkler Decl., ¶¶ 50-54).

As even further confirmation that Phares discloses the same first two alkylating and hydrolyzing steps to make treprostinil as that disclosed in the '393 Patent, Phares details the same procedures as were used to make treprostinil in the '117 Patent and Moriarty reference but applies them to make (-)-treprostinil, the enantiomer of (+) -treprostinil enantiomer. (Phares, Ex. 1005, p. 42). Phares explains that "enantiomers of these compounds (including (-)-treprostinil) can be synthesized using the reagents and synthons of enantiomeric chirality of the above reagents," referring to the reaction scheme where "the enantiomer of the commercial drug (+)-Treprostinil was synthesized using the stereoselective intramolecular Pauson Khand reaction as a key step and Mitsunobu inversion of the side-chain hydroxyl group." (Ex. 1005, p. 42). Phares details the exact same alkylation and hydrolyzing steps (both included in Phares as "step (l)"). (Ex. 1005, p. 42). This is the identical procedure claimed in steps (a) and (b). (*Compare* Ex. 1005, p 42, "(1) i. $C1CH_2CN$, K_2CO_3. ii, KOH, CH_3OH, reflux. 83 % (2 steps)," with '393 Patent (Ex. 1001), Claim 1 steps (a) and (b) and '393 Patent col. 9 line 25 – col.11, line 37 ('393 Patent, Examples 1 and 2).)

Phares discloses in its Claim 49 the identical, pharmaceutically acceptable treprostinil diethanolamine salt that Claim 1 claims:



(Phares, Ex. 1005, p. 99, Claim 49), which may be compared to the same structure claimed in Claim 1 and 9 and displayed as corresponding to these claims in the '393 Patent:



('393 Patent, Ex. 1001, col. 8, lines 50-64). Other than a change in formatting, these two structures from Phares and the '393 Patent are identical. *See also* (Ex. 1009, Winkler Decl. ¶¶ 50-53).

In the '393 Patent, treprostinil diethanolamine Form B was made directly from precipitation in a mixed solvent of ethanol and ethanol acetate. In Phares (Ex. 1005), treprostinil diethanolamine Form B is made by first generating Form A from any of many possible mixed solvents, and then converting Form A to Form B in a second mixed solvent. No claim in the '393 Patent specifies what solvents should be used, and thus, all of these procedures fall within the '393 Patent claims. In both the '393 Patent and Phares (Ex. 1005), treprostinil diethanolamine salt Form B is made. Phares demonstrated that Form B is the more stable form as compared to Form A. (Ex. 1005, pp. 88-93; Winkler Decl., ¶ 59). Phares further discloses a melting point of 107º C (Ex. 1005, p. 91 & Fig. 21) for the Form B salt. The '393 Patent, however, discloses lower and broader melting point ranges for the Form B salt in the ranges of 104.3-106.3º C (Batch No. 1) and 104.7-106.6º C (Batch No. 3) (Ex. 1001, col. 12, line 65 – col. 13, line 11, Example 3), as well as 105.0-106.5º C (Batch No. 1) and 104.5-105.5 ºC (Batch No. 2) (Ex. 1001, col. 13, line 59, Example 4); *see also* (Ex. 1001, col. 12, lines 53-55 (noting Form B requires a melting point of the treprostinil diethanolamine salt of more than 104º C). The higher melting point disclosed in Phares is consistent with higher purity for the product of Phares than the '393 Patent's product. (Ex. 1009, Winkler Decl., ¶ 60). As Phares necessarily discloses a higher purity of treprostinil diethanolamine as is disclosed and claimed in the '393 Patent, Phares inherently anticipates the '393 Patent's claims. *See also* (Ex. 1009, Winkler Decl., ¶ 62).

Additionally, Claim 1 claims both treprostinil diethanolamine salt and treprostinil free acid. The step

of reacting the foregoing salt with an acid to form the compound of Formula I in Claim 1 of the '393 Patent (Ex. 1001) is optional. Therefore, no disclosure in Ex. 1005 is required to demonstrate anticipation of Claim 1. Moreover, the '393 Patent admits that step (d) is merely a "simple acidification with diluted hydrochloric acid" step, and not a novel step. (Ex. 1001 col.17, lines 34-36.)

Claim 2

'393 Patent Claim Element	**Prior Art Disclosure**
2. The product of claim 1, wherein the purity of compound of formula I in said product is at least 99.5%.	*See* disclosure for Claim 1.

As Phares discloses the same product and process of Claim 1, including making the most stable crystal form, Form B, of a higher melting point than that disclosed in the '393 Patent, as discussed *supra*, Phares necessarily discloses a salt of at least 99.5% purity. (Ex. 1009, Winkler Decl., ¶ 62).

Additionally, the degree of purity of 99.5% recited in Claim 2 is actually 0.2% ***less*** than the 99.7% reported by Moriarty (Ex. 1004, p. 13) – well within experimental error. (Ex. 1009, Winkler Decl., ¶¶ 69-70). Patent Owner submitted a declaration from inventor Dr. David Walsh, which contended that the prior art Moriarty reference produced a purity level of only 99.4%, contrary to the 99.7% actually recited in Moriarty. (Ex. 1002-2, p. 347). Dr. Walsh does not explain what process conditions mattered in gaining the 99.4% result. (Ex. 1009, Winkler Decl., ¶ 67).

Nevertheless, even if it were true that the prior art's purity level was only 99.4% instead of 99.7%, the difference between 99.4% and 99.5% is well within experimental error, as explained by Dr. Winkler. (Ex. 1009, Winkler Decl., ¶¶ 69-70). This 0.1% difference would not represent a significant deviation from the processes of the prior art in light of experimental error in the detection method that is used when high-liquid chromatography (HPLC) is used to determine levels of impurities. (*Id.,* at ¶ 68*).* Indeed, even a difference of 0.2% between the claimed processes of the '393 Patent and the prior art, such as Moriarty (Ex. 1004), would be attributable to experimental error, and thus the claimed degree of purity under the claimed processes of the '393 Patent would present no distinction from the art. The '393 Patent itself discloses a purity of the claimed compound of 100.4% (Ex. 1001, col. 13, line 64), indicating, as Dr. Winkler notes, there the deviation in the reported data of ± 0.4% reflects a minimum deviation for the equipment the inventors used. (Ex. 1009, Winkler Decl., ¶ 70).

Claim 3

'393 Patent Claim Element	**Prior Art Disclosure**
3. The product of claim 1, wherein the alkylating agent is $Cl(CH_2)_wCN$, $Br(CH_2)_wCN$, or $I(CH_2)_wCN$.	Ex. 1005, p. 42 ($Cl(CH_2)_wCN$).

Phares discloses the alkylating agent is $ClCH_2CN$ which corresponds to $Cl(CH_2)_wCN$ where w is 1. (Ex. 1005, p. 42).

Claim 4

'393 Patent Claim Element	**Prior Art Disclosure**
4. The product of claim 1, wherein the base in step (b) is KOH or NaOH.	Ex. 1005, p. 42 (KOH).

Phares discloses that the base in step (b) is KOH. (Ex. 1005, p. 42).

Claim 5

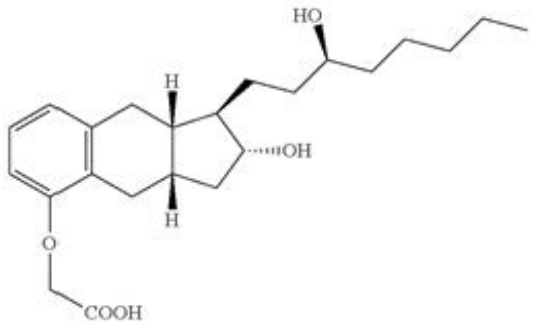
'393 Patent Claim Element	**Prior Art Disclosure**
5. The product of claim 1, wherein the base B in step (c) is selected from the group consisting of ammonia, N-methylglucamine, procaine, tromethamine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.	Ex. 1005, p. 24; pp. 57-58; p. 99, Claim 49.

Phares discloses the use of the base diethanolamine. (Ex. 1005, p. 24; p. 99, Claim 49). Phares (Ex. 1005, pp. 57-58) also discloses several other bases such as ammonia, magnesium, lysine, arginine and triethanolamine, all of which are recited in Claim 5 of the '393 Patent (Ex. 1001).

Claim 7

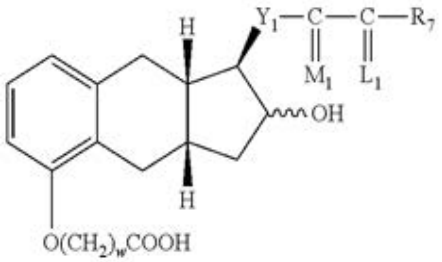
'393 Patent Claim Element	**Prior Art Disclosure**
7. The product of claim 1, wherein Y_1 is —CH_2CH_2—; M_1 is α-OH:β-H or α-H:β-OH; —$C(L_1)$-R_7 taken together is — $(CH_2)_4CH_3$; and w is 1.	*See* disclosure for Claim 1.

As discussed above, Phares (Ex. 1005) discloses a synthesis of treprostinil which has the following structure:



(*see e.g.,* Phares, Ex. 1005, pp. 41-42).

And the product (*i.e.*, Formula I) of Claim 1 of the '393 Patent (Ex. 1001) has the following generic structure:



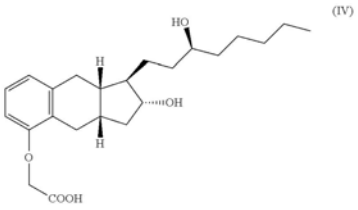
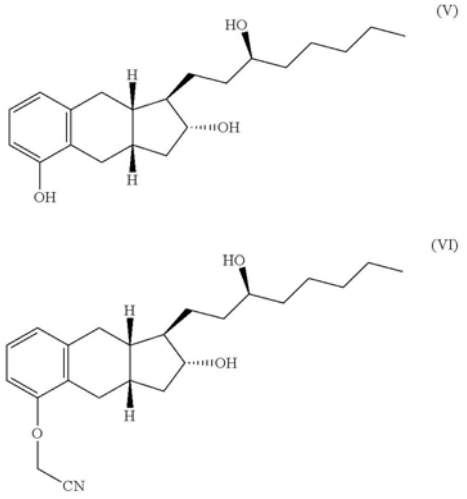
In treprostinil, Y_1 is —CH_2CH_2—; M_1 is a H and a OH group in the S configuration; —$C(=L_1)$-R_7 taken together is —$(CH_2)_4CH_3$; and w is 1. Therefore, the requirements of Claim 7 are satisfied.

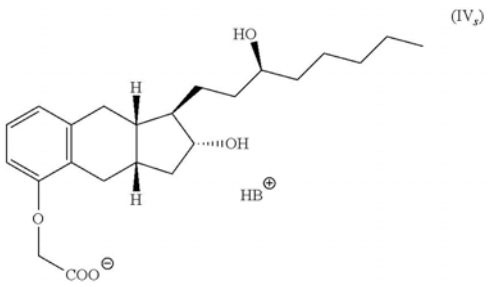
Claim 8

'393 Patent Claim Element	**Prior Art Disclosure**
8. The product of claim 1, wherein the process does not include purifying the compound of formula (III) produced in step (a).	Ex. 1005, pp. 41-42.

As discussed above, Phares (Ex. 1005, pp. 41-42) discloses that Formula 11b is converted to Formula 2 by treatment with the alkylating agent $ClCH_2CN$ followed by the base KOH. Phares' synthetic scheme, as disclosed on p. 42 (Ex. 1005), does not indicate that any intermediate compound is purified. Therefore, the requirements of Claim 8 are satisfied.

Claim 9

'393 Patent Claim Element	**Prior Art Disclosure**
9. (pre) A product comprising a compound having formula IV  or a pharmaceutically acceptable salt thereof, wherein the product is prepared by the process comprising	Ex. 1005, pp. 41-42 (enantiomer of Formula 2), pp. 85-93; p. 99, Claim 49.
9. (a) alkylating a compound of formula V with an alkylating agent to produce a compound of formula VI, 	Ex. 1005, pp. 41-42.

9. (b) hydrolyzing the product of formula VI of step (a) with a base,	Ex. 1005, pp. 41-42.
9. (c) contacting the product of step (h) [*sic*]with a base B to form a salt of formula IV_s, and 	Ex. 1005, p. 24; pp. 85-93; p. 99, Claim 49.
9. (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula IV.	No disclosure needed as this step is optional.

See explanation under Claim 1.

Claim 11

'393 Patent Claim Element	**Prior Art Disclosure**
11. The product of claim 9, wherein the alkylating agent is $ClCH_2CN$.	Ex. 1005, p. 42

See explanation under Claim 3.

Claim 12

'393 Patent Claim Element	**Prior Art Disclosure**
12. The product of claim 9, wherein the base in step (b) is KOH.	Ex. 1005, p. 42

See explanation under Claim 4.

Claim 13

'393 Patent Claim Element	**Prior Art Disclosure**
13. The product of claim 9, wherein the base B in step (c) is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethamine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.	Ex. 1005, p. 24; pp. 57-58; pp. 85-93; p. 99, Claim 49.

See explanation under Claim 5.

Claim 14

'393 Patent Claim Element	**Prior Art Disclosure**
14. The product of claim 9, wherein the base B is diethanolamine.	Ex. 1005, p. 24; p. 57; pp. 85-93; p. 99, Claim 49.

See explanations under Claims 1 and 5.

Claim 16

'393 Patent Claim Element	**Prior Art Disclosure**
16. The product of claim 9, wherein the process does not include purifying the compound of formula (VI) produced in step (a).	Ex. 1005, pp. 41-42.

See explanation under Claim 8.

Claim 17

'393 Patent Claim Element	**Prior Art Disclosure**
17. The product of claim 16, wherein the base B in step (c) is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethamine, magnesium, L-lysinc [*sic*], L-arginine, triethanolamine, and diethanolamine.	Ex. 1005, p. 24; pp. 57-58; pp. 85-93; p. 99, Claim 49.

See explanation under Claim 5.

Claim 18

'393 Patent Claim Element	**Prior Art Disclosure**
18. The product of claim 17, wherein the base B is diethanolamine.	Ex. 1005, p. 24; p. 57; pp. 85-93; p. 99, Claim 49.

See explanations under Claims 1 and 5.

Claim 19

'393 Patent Claim Element	**Prior Art Disclosure**
19. The product of claim 1, wherein the base in step (b) is KOH or NaOH and wherein the base 13 [*sic*] in step (c) is selected from the group consisting of ammonia. N-methyl glucamine, procaine, tromethamine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.	Ex. 1005, p. 24; p. 42; pp. 57-58; pp. 85-93; p. 99, Claim 49.

See explanations under Claims 4 and 5.

Claim 20

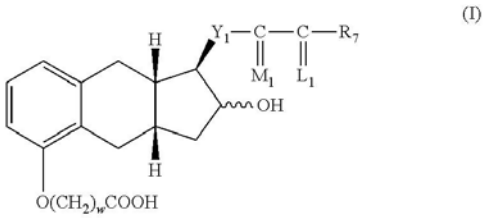
'393 Patent Claim Element	**Prior Art Disclosure**
20. The product of claim 9, wherein the base in step (b) is KOH or NaOH and wherein the base B in step (c) is selected from the group consisting of ammonia, N-methylglucamine, procaine, tromethamine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.	Ex. 1005, p. 24; p. 42; pp. 57-58; pp. 85-93; p. 99, Claim 49.

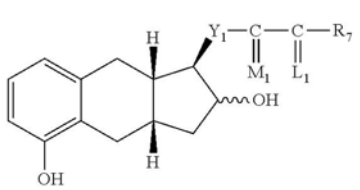
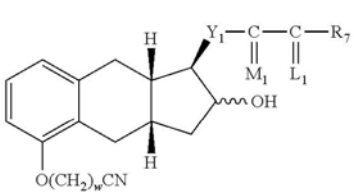
See explanations under Claims 4 and 5.

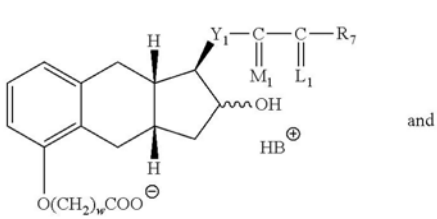
B. Ground 2: Detailed Explanation Under 37 C.F.R. § 42.104(b) of How Claims 1-5, 7-9, 11-14 and 16-20 are Obvious under 35 U.S.C. § 103(a) over Moriarty (Ex. 1004) with either Phares (Ex. 1005) or Kawakami (Exs. 1006 & 1007).

In addition to the anticipation challenges noted above, Claims 1-5, 7-9, 11-14, and 16-20 are rendered obvious under § 103 when considering Moriarty (Ex. 1004) in view of other prior art, including (but not limited to) either Phares (Ex. 1005) or Kawakami (Exs. 1006 & 1007).

Claim 1

'393 Patent Claim Element	**Prior Art Disclosure**
1. (pre) A product comprising a compound of formula I  (I) or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising	Ex. 1004, p. 3; p. 6 (w is 1, Y_1 is CH_2CH_2-, M_1 is a H and a OH group in the S configuration, L_1 is α-H; β-H, and R_7 is $–(CH_2)_3$-CH_3 in Formula 7).
1. (a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III,	Ex. 1004, p. 6; p. 13.

 (II)  (III) wherein w=1, 2, or 3; Y_1 is trans-CH=CH—, cis-CH=CH—, —$CH_2(CH_2)_m$—, or —C≡C—; m is 1, 2, or 3; R_7 is (1) —C_pH_{2p}—CH_3, wherein p is an integer from 1 to 5, inclusive, (2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different, (3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two	

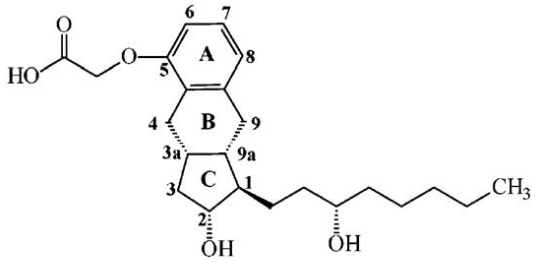
substituents are other than alkyl,(4) cis-CH=CH—CH_2—CH_3, (5) —$(CH_2)_2$—CH(OH)—CH_3, or (6) —$(CH_2)_3$—CH=C$(CH_3)_2$; —C(L_1)—R_7 taken together is (1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_5)alkyl; (2) 2-(2-furyl)ethyl, (3) 2-(3-thienyl)ethoxy, or (4) 3-thienyloxymethyl; M_1 is α-OH:β-R_5 or α-R_5β-OH or α-OR_1:β-R_5 or α-R_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group, and L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro,	
1. (b) hydrolyzing the product of formula III of step (a) with a base,	Ex. 1004, p. 6, p. 13.
1. (c) contacting the product of step (h) [*sic*] with a base B to form a salt of formula I_s.  (I_s) and	Ex. 1005, p. 24; pp. 85-93; p. 99, Claim 49; Ex. 1007, p. 6.

1. (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula I.	No disclosure needed as this step is optional; *see also* Ex. 1007, p. 6.

Moriarty (Ex. 1004) discloses the synthesis (at p. 6) of treprostinil which is Formula 7 on p. 3. Formula 7 on p. 3 of Moriarty (Ex. 1004) is equivalent to Formula I of Claim 1 of the '393 Patent (Ex. 1001, col. 17) in the case where w is 1, Y_1 is CH_2CH_2-, M_1 is a H and a OH group in the S configuration, L_1 is α-H; β-H, and R_7 is $–(CH_2)_3$-CH_3.

Formula 34 on p. 6 of Moriarty (Ex. 1004, p. 6, 13) is alkylated by $ClCH_2CN$ to yield Formula 35 on p. 6. Formula 34 corresponds to Formula II in Claim 1 of the '393 Patent (Ex. 1001) in the case where Y_1 is CH_2CH_2-, M_1 is a H and a OH group in the S configuration, L_1 is α-H; β-H, and R_7 is $–(CH_2)_3$-CH_3. Formula 35 corresponds to Formula III in Claim 1 of the '393 Patent (Ex. 1001, col. 18) in the case where Y_1 is CH_2CH_2-, M_1 is a H and a OH group in the S configuration, L_1 is α-H; β-H, R_7 is $–(CH_2)_3$-CH_3 and w is 1. Ex. 1004 at p. 13 discloses that Formula 35 is hydrolyzed with a base (*i.e.*, aqueous KOH, followed by acidification) to yield Formula 7 (Moriarty, Ex. 1004, p. 3, p. 6).

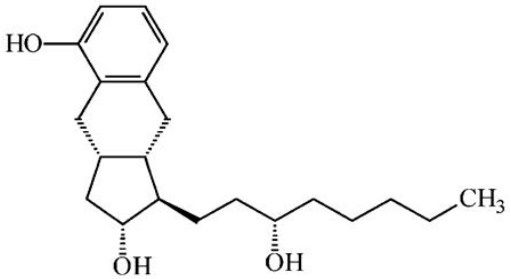
Formula 7 of Moriarty is as follows:



7

(Moriarty, Ex. 1004, p. 3, col. 1).

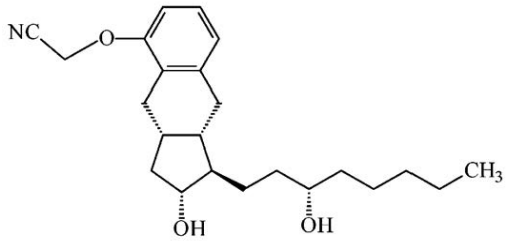
Formula 34 of Moriarty is as follows:



34

(Moriarty, Ex. 1004, p. 6).

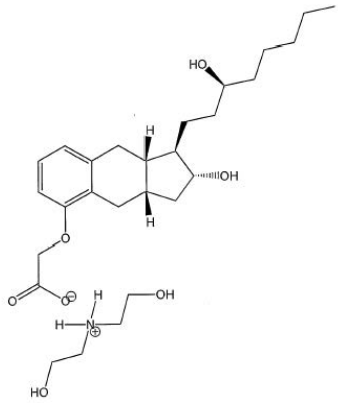
Formula 35 of Moriarty is as follows:



35

(Moriarty, Ex. 1004, p. 6).

While the step of reacting Formula 7 with a base to form a salt of Formula 7 is not disclosed in Moriarty (Ex. 1004), this step is disclosed in Phares (Ex. 1005). Phares (Ex. 1005, p. 24) discloses that treprostinil acid (which is equivalent to Formula 7 in Moriarty, Ex. 1004) is dissolved in a 1:1 molar ratio mixture of ethanol: water and diethanolamine (*i.e.*, the base) is added and dissolved. The solution is heated and acetone is added as an antisolvent during cooling. The resulting structure (below) corresponds to the salt of Formula I_s in Claim 1 of the '393 Patent (Ex. 1001):



(Phares, Ex. 1005, p. 99, Claim 49).

Petitioner notes that the formation of salts by the reaction of carboxylic acids with bases is a common reaction in organic chemistry and this process is well within the skill of one of ordinary skill in the art, as discussed above.

In addition, Kawakami discloses contacting a carboxylic acid of a prostacyclin derivative with a base to form a salt. (Exs. 1006 & 1007). Kawakami is directed to the preparation and use of dicyclohexylamine (i.e., a weak base similar in its reactivity to diethanolamine) to form a crystalline dicyclohexylamine salt of a methanoprostacyclin derivative. Ex. 1007, at p. 6, further discloses that the dicyclohexylamine salt of a methanoprostacyclin derivative can be easily reverted to the free methanoprostacyclin derivative by conventional methods. Furthermore, Kawakami (Ex. 1007) at p. 6 discloses that the salt that is obtained has fairly high purity and the purity can be further improved by recrystallization as needed with the use of an appropriate solvent.

A person of ordinary skill in the art would be motivated to combine Moriarty (Ex. 1004) with either Phares (Ex. 1005) or Kawakami (Exs. 1006, 1007). (Ex. 1009, Winkler Decl., ¶ 74). Moriarty discloses steps (a) and (b) of Claim 1 of the '393 Patent. (Ex. 1004, p. 6, 13). Phares discloses step (c) of Claim 1 of the '393 Patent (Ex. 1005, p. 24), while Kawakami discloses that prostacyclin compounds (an example of which includes treprostinil), can be purified by using weak bases and forming salts (Ex. 1007, p. 6). Further, if desired, Kawakami discloses that the product can be

turned back into the free acid as disclosed under the optional Claim 1(d). (*Id*.). Accordingly, a person of ordinary skill in the art would be motivated to combine Moriarty with either Phares or Kawakami to obtain a product of at least equal purity to that claimed in the '393 Patent. (Ex. 1009, Winkler Decl., ¶ 74).

Claim 2

'393 Patent Claim Element	**Prior Art Disclosure**
2. The product of claim 1, wherein the purity of compound of formula I in said product is at least 99.5%.	*See* disclosure for Claim 1.

As the combination of Moriarty (Ex. 1004) with either Phares (Ex. 1005) or Kawakami (Exs. 1006 & 1007) discloses the same process steps and product of the '393 Patent, the combination of these references would disclose a purity of at least equal purity to that claimed in the '393 Patent. (Ex. 1009, Winkler Decl., ¶ 76); *see also supra* (Section B, Claim 2 discussing Phares).

Additionally, and as discussed *supra*, the degree of purity of 99.5% recited in Claim 2 is actually 0.2% ***less*** than the 99.7% reported by Moriarty (Ex. 1004, p. 13) – well within experimental error. (Ex. 1009, Winkler Decl., ¶¶ 69-70). Patent Owner submitted a declaration from inventor Dr. David Walsh, which contended that the prior art Moriarty reference produced a purity level of only 99.4%, contrary to the 99.7% actually recited in Moriarty. (Ex. 1002-2, p. 347). Dr. Walsh does not explain what process conditions mattered in gaining the 99.4% result. (Ex. 1009, Winkler Decl., ¶ 67).

Nevertheless, even if it were true that the prior art's purity level was only 99.4% instead of 99.7%, the difference between 99.4% and 99.5% is well within experimental error, as explained by Dr. Winkler. (Ex. 1009, Winkler Decl., ¶¶ 69-70). This 0.1% difference would not represent a significant deviation from the processes of the prior art in light of experimental error in the detection method that is used when high-liquid chromatography (HPLC) is used to determine levels of impurities. (*Id*., at 68). Indeed, even a difference of 0.2% between the claimed processes of the '393 Patent and the prior art, such as Moriarty (Ex. 1004), would be attributable to experimental error, and thus the claimed degree of purity under the claimed processes of the '393 Patent would present no distinction from the art. The '393 Patent itself discloses a purity of the claimed compound of 100.4% (Ex. 1001, col. 13, line 64), indicating, as Dr. Winkler notes, there the deviation in the reported data of ± 0.4% reflects a minimum deviation for the equipment the inventors used. (Ex. 1009, Winkler Decl., ¶ 70).

Claim 3

'393 Patent Claim Element	**Prior Art Disclosure**
3. The product of claim 1, wherein the alkylating agent is $Cl(CH_2)_wCN$, $Br(CH_2)_wCN$, or $I(CH_2)_wCN$.	Ex. 1004, p. 3; p. 6 ($Cl(CH_2)_wCN$.

As discussed above, Moriarty (Ex. 1004, p. 3 and p. 6) discloses that the alkylating agent is $ClCH_2CN$ which corresponds to $Cl(CH_2)_wCN$ where w is 1.

Claim 4

'393 Patent Claim Element	**Prior Art Disclosure**
4. The product of claim 1, wherein the base in step (b) is KOH or NaOH.	Ex. 1004, p. 3; p. 6 (KOH).

As discussed above, Moriarty (Ex. 1004, p. 6) discloses that the base in step (b) is KOH.

Claim 5

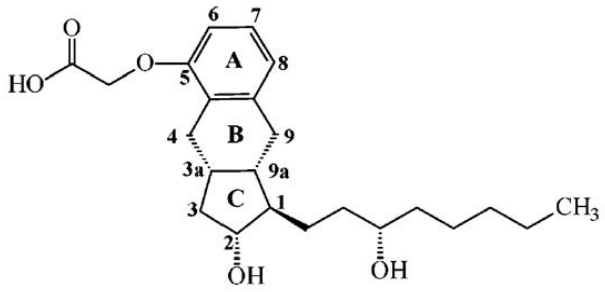
'393 Patent Claim Element	**Prior Art Disclosure**
5. The product of claim 1, wherein the base B in step (c) is selected from the group consisting of ammonia, N-methylglucamine, procaine, tromethamine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.	Ex. 1004, p. 6; p. 13; Ex. 1005, p. 24; pp. 57-58; pp. 85-93; p. 99, Claim 49; Ex. 1007, pp. 5-6.

As discussed above, Phares (Ex. 1005, p. 24; p. 99, Claim 49) discloses the use of the base diethanolamine. In addition, Phares (Ex. 1005, pp. 57-58) discloses several other bases that include ammonia, magnesium, lysine, arginine and triethanolamine, all of which are recited in Claim 5 of the '393 Patent (Ex. 1001).

Claim 7

'393 Patent Claim Element	**Prior Art Disclosure**
7. The product of claim 1, wherein Y_1 is —CH_2CH_2—; M_1 is α-OH:β-H or α-H:β-OH; —$C(L_1)$-R_7 taken together is — $(CH_2)_4CH_3$; and w is 1.	*See* disclosure for Claim 1.

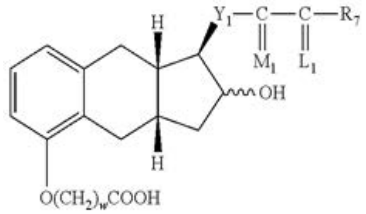
As discussed above, the combination of references discloses a synthesis of treprostinil which has the following structure:



7

(*see e.g.,* Moriarty, Ex. 1004, col. 1, p. 3).

And the product (*i.e.*, Formula I) of Claim 1 of the '393 Patent (Ex. 1001) has the following generic structure:



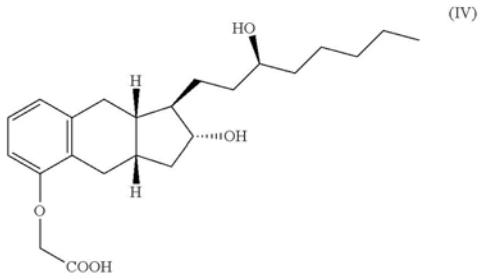
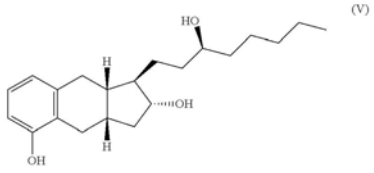
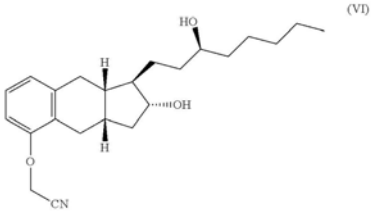
In treprostinil, Y_1 is —CH_2CH_2—; M_1 is a H and a OH group in the S configuration; —$C(L_1)$-R_7 taken together is —$(CH_2)_4CH_3$; and w is 1. Therefore, the requirements of Claim 7 are satisfied.

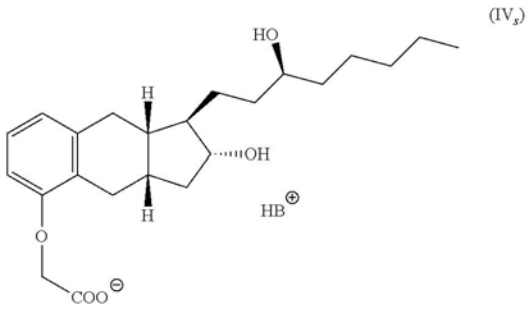
Claim 8

'393 Patent Claim Element	**Prior Art Disclosure**
8. The product of claim 1, wherein the process does not include purifying the compound of formula (III) produced in step (a).	Ex. 1004, p. 6; p. 13; Ex. 1005, pp. 41-42

Moriarty (Ex. 1004, p. 6 and p. 13) discloses that Formula 35 (which corresponds to Formula III in Claim 1 of the '393 Patent (Ex. 1001)) is purified. However, Phares (Ex. 1005) discloses that the purification of Formula 35 (as described in Moriarty) would not be necessary. Specifically, Phares (Ex. 1005, pp. 41-42) discloses that Formula 11b is converted to Formula 2 by treatment with the alkylating agent $ClCH_2CN$ followed by the base KOH. The synthetic scheme of Phares (p. 42) does not indicate that any intermediate compound is purified. In view of the foregoing, one of ordinary skill in the art would understand that the treatment of Formula 11b with the alkylating agent could be followed by the hydrolysis with a base without purifying the product of the alkylation reaction. Furthermore, a person of ordinary skill in the art would be motivated to combine Phares (Ex. 1005, p. 42) with the teachings of Moriarty (Ex. 1004, p. 6; p. 13), since shortening the number of synthetic steps should increase efficiency and presumably lower costs. *See also* (Ex. 1009, Winkler Decl., ¶¶ 77-78).

Claim 9

'393 Patent Claim Element	**Prior Art Disclosure**
9. (pre) A product comprising a compound having formula IV  (IV) or a pharmaceutically acceptable salt thereof, wherein the product is prepared by the process comprising	Ex. 1004, p. 6
9. (a) alkylating a compound of formula V with an alkylating agent to produce a compound of formula VI,  (V)  (VI)	Ex. 1004, p. 6; p. 13

9. (b) hydrolyzing the product of formula VI of step (a) with a base,	Ex. 1004, p. 6; p. 13
9. (c) contacting the product of step (h) [*sic*] with a base B to form a salt of formula IV_s, and 	Ex. 1004, p. 6; p. 13; Ex. 1005, p. 24; pp. 85-93; p. 99, Claim 49; Ex. 1007, pp. 5-6
9. (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula IV.	No disclosure needed as this step is optional

See explanation under Claim 1.

Claim 11

'393 Patent Claim Element	**Prior Art Disclosure**
11. The product of claim 9, wherein the alkylating agent is $ClCH_2CN$.	Ex. 1004, p. 6; p. 13

See explanation under Claim 3.

Claim 12

'393 Patent Claim Element	**Prior Art Disclosure**
12. The product of claim 9, wherein the base in step (b) is KOH.	Ex. 1004, p. 6; p. 13

See explanation under Claim 4.

Claim 13

'393 Patent Claim Element	**Prior Art Disclosure**
13. The product of claim 9, wherein the base B in step (c) is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethamine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.	Ex. 1004, p. 6; p. 13; Ex. 1005, p. 24; pp. 57-58; pp. 85-93; p. 99, Claim 49; Ex. 1007, pp. 5-6

See explanation under Claim 5.

Claim 14

'393 Patent Claim Element	**Prior Art Disclosure**
14. The product of claim 9, wherein the base B is diethanolamine.	Ex. 1004, p. 6; p. 13; Ex. 1005, p. 24; pp. 57-58; pp. 85-93; p. 99, Claim 49; Ex. 1007, pp. 5-6

See explanations under Claims 1 and 5.

Claim 16

'393 Patent Claim Element	**Prior Art Disclosure**
16. The product of claim 9, wherein the process does not include purifying the compound of formula (VI) produced in step (a).	Ex. 1004, p. 6; p. 13

See explanation under Claim 8.

Claim 17

'393 Patent Claim Element	**Prior Art Disclosure**
17. The product of claim 16, wherein the base B in step (c) is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethamine, magnesium, L-lysinc [*sic*], L-arginine, triethanolamine, and diethanolamine.	Ex. 1004, p. 6; p. 13; Ex. 1005, p. 24; pp. 57-58; pp. 85-93; p. 99, Claim 49

See explanation under Claim 5.

Claim 18

'393 Patent Claim Element	**Prior Art Disclosure**
18. The product of claim 17, wherein the base B is diethanolamine.	Ex. 1004, p. 6; p. 13; Ex. 1005, p. 22; p. 57; pp. 85-93; p. 99, Claim 49

See explanations under Claims 1 and 5.

Claim 19

'393 Patent Claim Element	**Prior Art Disclosure**
19. The product of claim 1, wherein the base in step (b) is KOH or NaOH and wherein the base 13 [*sic*] in step (c) is selected from the group consisting of ammonia. N-methyl glucamine, procaine, tromethamine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.	Ex. 1004, p. 6; p. 13; Ex. 1005, p. 24; pp. 57-58; pp. 85-93; p. 99, Claim 49; Ex. 1007, pp. 5-6

See explanations under Claims 4 and 5.

Claim 20

'393 Patent Claim Element	**Prior Art Disclosure**
20. The product of claim 9, wherein the base in step (b) is KOH or NaOH and wherein the base B in step (c) is selected from the group consisting of ammonia, N-methylglucamine, procaine, tromethamine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.	Ex. 1004, p. 6; p. 13; Ex. 1005, p. 24; pp. 57-58; pp. 85-93; p. 99, Claim 49; Ex. 1007, pp. 5-6

See explanations under Claims 4 and 5.

C. Ground 3: Detailed Explanation Under 37 C.F.R. § 42.104(b) of How Claims 6, 10, 15, 21 and 22 are Obvious under 35 U.S.C. § 103(a) over Moriarty (Ex. 1004) with Phares (Ex.

1005) or Kawakami (Exs. 1006 & 1007) and in further combination with Ege (Ex. 1008).

Claim 6

'393 Patent Claim Element	**Prior Art Disclosure**
6. The product of claim 1, wherein the acid in step (d) is HCl or H_2SO_4.	Ex. 1004, p. 6; p. 13; Ex. 1007, pp. 5-6; Ex. 1008, p. 8

As discussed above, Phares (Ex. 1005, p. 22) discloses forming the treprostinil diethanolamine salt. Also, as discussed above, Kawakami (Exs. 1006 & 1007) discloses forming a crystalline dicyclohexylamine salt of a methanoprostacyclin derivative. Kawakami (Ex. 1007, p. 6) further discloses that the dicyclohexylamine salt of a methanoprostacyclin derivative "can be easily reverted to the free methanoprostacyclin derivative by *conventional methods*" (emphasis added). In addition, Kawakami (Ex. 1007) at p. 6 discloses that the salt that is obtained has fairly high purity and the purity can be further improved by recrystallization as needed with the use of an appropriate solvent.

A person of ordinary skill in the art would understand that one such conventional method for converting the dicyclohexylamine salt of a methanoprostacyclin derivative to the free methanoprostacyclin derivative, or converting the treprostinil diethanolamine salt to treprostinil (*i.e.*, the free acid) is by treating the salt with a strong acid such as HCl or H_2SO_4. *See* (Ex. 1009, Winkler Decl., ¶ 84).

As further evidence as to the conventional nature of such a conversion, Petitioner also notes that Ege (Ex. 1008, p. 8) discloses that sodium benzoate (*i.e.*, a carboxylate salt) can be converted back to benzoic acid (*i.e.*, a carboxylic acid) by treatment with the acid HCl. *See* (Ex. 1009, Winkler Decl., ¶ 86).

A person of ordinary skill in the art would be motivated to include the carboxylate salt formation and regeneration of the neutral carboxylic acid with the syntheses of Moriarty (Ex. 1004, p. 6; p. 13) and Phares (Ex. 1005, p. 24), since Kawakami (Ex. 1007, p. 6) discloses that "the dicyclohexylamine salt obtained by the present invention can be easily reverted to a free methanoprostacyclin derivative [I] by conventional methods, and the resulting methanoprostacyclin derivative exhibits excellent crystallinity compared with substances not purified according to the present invention." Accordingly, a person of ordinary skill in the art would want to form the treprostinil diethanolamine salt, purify it, and then convert it back to its free form (*i.e.*, treprostinil) in order to obtain excellent crystallinity and increased purity. (Ex. 1009, Winkler Decl., ¶ 88). And Ege (Ex. 1008, p. 8) teaches that one such method for obtaining the free form of any carboxylic acid (including treprostinil) would be by treatment of the corresponding carboxylate salt with a strong acid. *See also* (Ex. 1009, Winkler Decl., ¶ 88).

Claim 10

'393 Patent Claim Element	**Prior Art Disclosure**
10. The product of claim 9, wherein the purity of product of step (d) is at least 99.5%.	Ex. 1004, p. 6; p. 13; Ex. 1007, pp. 5-6; Ex. 1008, p. 8

The combination of Moriarty (Ex. 1004) and Phares (Ex. 1005) (or Kawakami, Exs. 1006 & 1007) and Ege (Ex. 1008) would disclose that the purity of treprostinil of at least equal purity to that of the '393 Patent, since the combination of these references discloses the same product and same process of Claim 9. (Ex. 1009, Winkler Decl., ¶ 89). As Dr. Winkler explains, as Phares (Ex. 1005) discloses the same polymorph Form B and a higher melting point than that disclosed in the '393 Patent, Phares discloses an even higher purity than that disclosed in the '393 Patent. (Ex. 1009, Winkler Decl., ¶¶ 58-60). Indeed, as discussed *supra*, Moriarty actually reports that the treprostinil made by Moriarty had 99.7% purity (Ex. 1004, p. 13) - although Patent Owner submitted a declaration from inventor Dr. David Walsh, which contended that the prior art Moriarty reference produced a purity level of only 99.4%, contrary to the 99.7% actually recited in Moriarty. (Ex. 1002-2, p. 347). Dr. Walsh does not explain what process conditions mattered in gaining the 99.4% result, and, moreover, there may be significant batch-to-batch variation based on the limited sample set provided. (Ex. 1009, Winkler Decl., ¶¶ 66). Nevertheless, even if it were true that the prior art's purity level was only 99.4% instead of 99.7%, the difference between 99.4% and 99.5% is well within

experimental error, as noted by Dr. Winkler. (Ex. 1009, Winkler Decl., ¶¶ 69-70).

Claim 15

'393 Patent Claim Element	**Prior Art Disclosure**
15. The product of claim 9, wherein the acid in step (d) is HCl.	Ex. 1004, p. 6; p. 13; Ex. 1007, pp. 5-6; Ex. 1008, p. 8

See explanation under Claim 6.

Claim 21

'393 Patent Claim Element	**Prior Art Disclosure**
21. The product of claim 1, wherein step (d) is performed.	Ex. 1004, p. 6; p. 13; Ex. 1007, pp. 5-6; Ex. 1008, p. 8

See explanation under Claim 6.

Claim 22

'393 Patent Claim Element	**Prior Art Disclosure**
22. The product of claim 21, wherein the product comprises a pharmaceutically acceptable salt formed from the product of step (d).	Ex. 1004, p. 6; p. 13; Ex. 1007, pp. 5-6; Ex. 1008, p. 8

Claim 22 recites that the "product of Claim 21, wherein the product comprises a pharmaceutically

acceptable salt formed from the product of step (d)." The product of Claim 21 (which recites, the "product of Claim 1, wherein step (d) is performed) is a free carboxylic acid. Claim 22, therefore, effectively recites that a carboxylate salt (*i.e.,* a pharmaceutically acceptable salt) can be formed from a free carboxylic acid, which was well-known in the art prior to December 17, 2007. (*See* explanation under Claim 6).

X. CONCLUSION

In view of the foregoing, Petitioner respectfully requests that trial for *inter partes* review be instituted on Claims 1-22 of the '393 Patent, and those claims be canceled as invalid.

Date: October 1, 2015

Respectfully submitted,

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