UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

LIQUIDIA TECHNOLOGIES, INC.,

Petitioner

v.

UNITED THERAPEUTICS CORPORATION,

Patent Owner

U.S. Patent No. 9,593,066

Issue Date: March 14, 2017

Title: Process to Prepare Treprostinil, the Active Ingredient in Remodulin®

~~DECLARATION OF JEFFREY D. WINKLER, PH.D.~~
~~IN SUPPORT OF~~ PETITION FOR *INTER PARTES* REVIEW
OF U.S. Patent No. 9,593,066

~~VI.~~ IV. SUMMARY ~~OVERVIEW~~ OF THE '066 PATENT

A. Brief Description of the '066 Patent

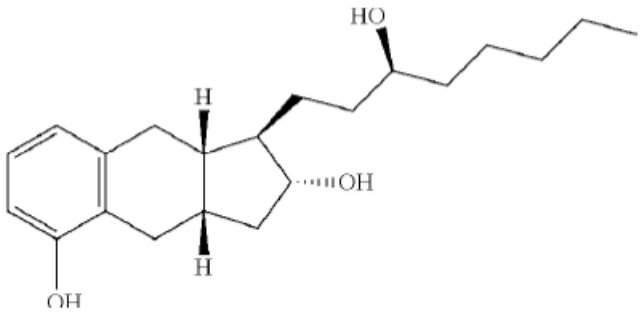
~~I understand that the~~ The '066 patent is entitled "Process to Prepare Treprostinil, the Active Ingredient in Remodulin®." The claims of the '066 patent are product-by-process claims. These claims include two independent (claims 1 and 8) and eight dependent claims.

The '066 patent discloses an "improved process" to prepare prostacyclin derivatives such as treprostinil. (Ex. 1001, Abstract.) Claim 1 is drawn to a pharmaceutical composition comprising treprostinil or a pharmaceutically acceptable salt thereof. Claim 8 is drawn to a process of preparing the same product from claim 1, comprising the steps of alkylation of an intermediate triol ~~and hydrolyzing~~ to form a treprostinil ~~or a pharmaceutically acceptable~~ salt ~~thereof~~. *(Id., claims* 1 and 8.)

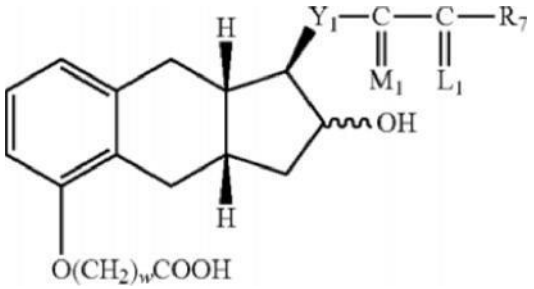
Each of the independent claims include limitations that the claimed pharmaceutical composition~~/product~~ is made by a process comprising: (a) providing a starting batch of treprostinil having one or more impurities resulting from prior alkylation and hydrolysis steps; (b) forming a treprostinil salt by adding a base; and (c) preparing a pharmaceutical composition~~/product~~ comprising treprostinil or a pharmaceutically acceptable salt thereof from the isolated treprostinil salt.

~~The claim limitations of the '066 patent are as follows:~~

	Claim Limitation
1 [a]	A pharmaceutical composition comprising treprostinil or a pharmaceutically acceptable salt thereof,
1[b]	said composition prepared by a process comprising:
1 [c]	providing a starting batch of treprostinil having one or more impurities resulting from prior alkylation and hydrolysis steps,
1 [d]	forming a salt of treprostinil by combining the starting batch and a base,

1 [e]	isolating the treprostinil salt, and
1 [f]	preparing a pharmaceutical composition comprising treprostinil or a pharmaceutically acceptable salt thereof from the isolated treprostinil salt,
1 [g]	whereby a level of one or more impurities found in the starting batch of treprostinil is lower in the pharmaceutical composition, and
1 [h]	wherein said alkylation is alkylation of benzindene triol.
2	The pharmaceutical composition of claim 1, wherein the salt is isolated in crystalline form.
3	The pharmaceutical composition of claim 1, wherein the base is selected from the group consisting of sodium, ammonia, potassium, calcium, ethanolamine, diethanolamine, N-methylglucamine, and choline.
4	The pharmaceutical composition of claim 3, wherein the base is diethanolamine.
5	The pharmaceutical composition of claim 1, wherein the base is combined with treprostinil that has not been previously isolated.
6	The pharmaceutical composition of claim 1, wherein the isolated salt is stored at ambient temperature.
7	The pharmaceutical composition of claim 1, which is a pharmaceutical solution.
8[a]	A process of preparing a pharmaceutical product comprising treprostinil or a pharmaceutically acceptable salt thereof, comprising:
8[b]	Alkylating a triol intermediate of the formula: 
8[c]	hydrolyzing the resulting compound to form treprostinil,
8[d]	forming a salt of treprostinil stable at ambient temperature,
8[e]	storing the treprostinil salt at ambient temperature, and
8[f]	preparing a pharmaceutical product from the treprostinil salt after storage,
8[g]	wherein the pharmaceutical product comprises treprostinil or a pharmaceutically acceptable salt thereof
9	A pharmaceutical product prepared by the process of claim 8.
10	The process as claimed in claim 8, wherein forming the salt of treprostinil stable at ambient temperature is performed by adding diethanolamine to treprostinil.

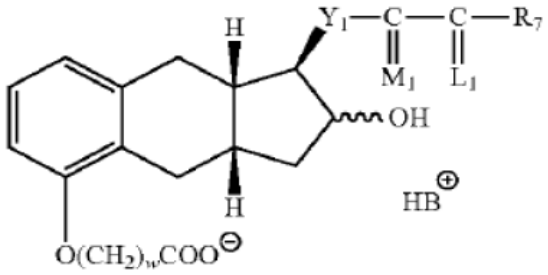
~~The~~ More specifically, the '066 patent discloses a process for the preparation of a compound of Formula I (which includes treprostinil) shown below~~,~~:



(Ex. 1001 at col. 2:7-21~~), where~~.) Where: 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; M_1 is α-OH: β-R_5 or α-R_5: β-OH or α-OR_2: β-R_5 or α-R_5: β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group; L_1 is α-R3: β-R4, α-R4: β -R3, or a mixture of α-R_3: 13-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; and 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, (Ci-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$(CH_3)_2$~~,~~; wherein —$C(L_1)$-R_7^2 taken together is: (1) (C4-C7)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. *(Id. at* cols. 2:46-3:15.)~~ Treprostinil is the specific~~

~~Formula I compound where w = 1; Y_1 is —$CH_2(CH_2)_m$— and m is 1; M_1 is α-OH: (β-R_5 or α-R_5: β-OH, wherein R_5 is hydrogen; 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 R4 are hydrogen; and R_7 is —C_pH_{2p}—CH_3, wherein p is an integer from 1 to 5 inclusive (p=3).~~

The '066 patent discloses alkylating the treprostinil ~~precursor (benzindene triol, a.k.a. treprostinil triol)~~ with an alkylating agent and then hydrolyzing with a base. (*Id. at* col. 2:7-3:17.) The '066 patent further discloses contacting the product from the alkylation and hydrolysis steps with a base to form a salt (*e.g.* using the base diethanolamine to form treprostinil diethanolamine salt) of Formula Is shown below ~~(where B is diethanolamine and where the other variables are the same as for the treprostinil-specific version of Formula I explained in the previous paragraph)~~:[1]



(*Id. at* col. 3:19-30.) The treprostinil salt can then be reacted with an acid to form the compound of Formula 1 (treprostinil ~~-specific Formula I~~). (*Id. at* col. 3:31-33.) Formula 1 is at least 90.0%, 95.0%, or 99.0% pure. (*Id. at* col. 9:22-23.)

~~Formula I is a general formula, while Formula IV is specifically treprostinil. Formula IV, which is treprostinil, is disclosed to be at least 90.0%, 95.0%, or 99.0% pure. (*Id. at* col. 9:22-23.)~~

[1] Though the patent recites —C(L_1)-R_2, a POSA would understand this to be a typo. It should be "—C(L_1)-R_7" because the patent teaches that L_1 and R_7 can be taken together to form a "cycloalkyl," which a POSA would understand to be a ring. (Ex. 1001 at col. 3:2.)

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