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Paper 11
Entered: November 29, 2017

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MICRO LABS LIMITED and
MICRO LABS USA INC.,
Petitioner,

v.

SANTEN PHARMACEUTICAL CO., LTD. and
ASAHI GLASS CO., LTD.,
Patent Owner.

Case IPR2017-01434
Patent 5,886,035

Before LORA M. GREEN, JO-ANNE M. KOKOSKI, and CHRISTOPHER G. PAULRAJ, *Administrative Patent Judges.*

KOKOSKI, *Administrative Patent Judge.*

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

I. INTRODUCTION

Micro Labs Limited and Micro Labs USA Inc. (collectively, "Petitioner") filed a Petition ("Pet.") to institute an *inter partes* review of claims 1–14 of U.S. Patent No. 5,886,035 ("the '035 patent," Ex. 1001). Paper 1. Santen Pharmaceutical Co., Ltd. and Asahi Glass Co., Ltd. (collectively, "Patent Owner") filed a Preliminary Response ("Prelim. Resp."). Paper 10.

Institution of an *inter partes* review is authorized by statute when "the information presented in the petition . . . and any response . . . 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." 35 U.S.C. § 314; *see* 37 C.F.R. §§ 42.4, 42.108. Upon consideration of the Petition and Preliminary Response, and the evidence of record, we determine that Petitioner has demonstrated a reasonable likelihood of prevailing with respect to the unpatentability of claims 1–14 of the '035 patent. Accordingly, we institute an *inter partes* review of those claims.

A. Related Proceedings

The parties indicate that the '035 patent is being asserted in *Santen Pharmaceutical Co., Ltd. v. Micro Labs Limited*, Case No. 16-cv-00353 (D. Del. 2016) and *Santen Pharmaceutical Co., Ltd. v. Sandoz Inc.*, Case No. 16-cv-00354 (D. Del. 2016). Pet. 4; Paper 3, 1.

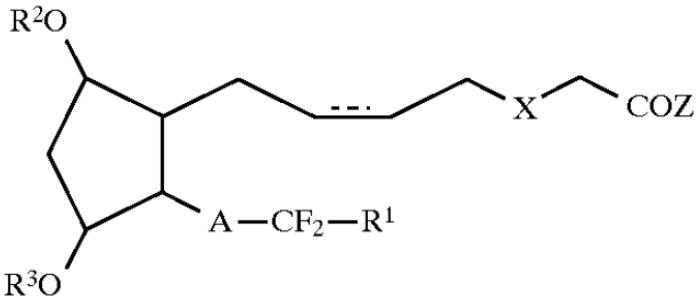
B. The '035 Patent

The '035 patent, titled "Difluoroprostaglandin Derivatives and Their Use," is directed to "fluorine-containing prostaglandin derivatives having two fluorine atoms at the 15-position (or their salts) and medicines containing the compounds as an active ingredient, particularly, preventative

or therapeutic medicines for eye diseases." Ex. 1001, 1:4–8. These compounds are derivatives of a class of prostaglandins referred to as "prostaglandin Fs" or "PGFs." *Id.* at 1:11–21, 61–63. The '035 patent states that, although naturally-occurring prostaglandin Fs "are known to lower intraocular pressure when topically applied to the eye," they are also "irritant to the eye and have a problem of their inflammatory side effects such as congestion and damage to the cornea" (*id.* at 1:12–19), and "extensive research has been conducted both at home and abroad for development of long-lasting PGF derivatives having much the same biological activities as the naturally occurring one and few side effects" (*id.* at 1:44–47).

In that regard, the '035 patent discloses that "15,15-difluoro-15-deoxy-$PGF_{2\alpha}$ and its derivatives are superior to the known natural $PGF_{2\alpha}$ in the effect of lowering intraocular pressure[,] are scarcely irritant to the eye, scarcely affect the ocular tissues such as the cornea, the iris, and the conjunctive, and have long-lasting efficacy." *Id.* at 2:7–12. The disclosed fluorine-containing prostaglandin derivatives also "are unlikely to decompose through metabolic processes such as hydrolysis and oxidation and [are] stable in the body," and "hardly stimulate melanogenesis." *Id.* at 19:21–28. As a result, "the medicine of the present invention is effective as a therapeutic agent, particularly for glaucoma or ocular hypertension." *Id.* at 29–31.

The fluorine-containing prostaglandin derivatives disclosed in the '035 patent have the following generic formula:

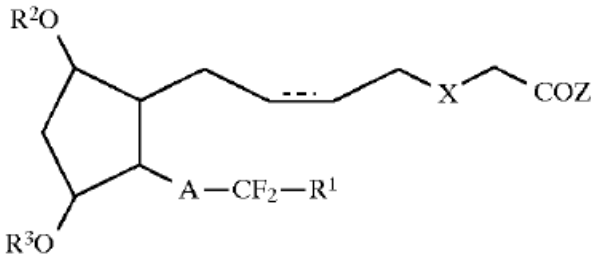


Ex. 1001, 2:20–29. These fluorine-containing derivatives "may be the same as the naturally occurring type except for the two fluorine atoms at the 15-position", i.e., "compounds wherein A is a vinylene group, R^1 is a n-pentyl group, both R^2 and R^3 are hydrogen atoms, X is $–CH_2–$, Z is –OH, and the dual line is a cis-double bond." *Id.* at 2:53–58. The '035 patent further teaches that fluorine-containing prostaglandin derivatives "having an ω-chain which is not of the naturally[-]occurring type (namely, wherein A is a vinylene group, and R^1 is a n-pentyl group) are preferred." *Id.* at 2:59–62; *see also id.* at 4:11–7:53 (setting forth compounds for A, X, R^1–R^7, and Z that "are preferred from the standpoint of biological activities and physical properties").

C. Challenged Claims

Petitioner challenges claims 1–14 of the '035 patent. Claims 1 and 12 are the only independent claims, and are reproduced below.

> 1. A fluorine-containing prostaglandin derivative of the following formula (1) or a salt thereof:



(1)

wherein A is an ethylene group, a vinylene group, an ethylene group, $–OCH_2–$ or $–SCH_2–$,

R^1 is a substituted or unsubstituted aryloxyalkyl group,

each of R^2 and R^3 which are independent of each other, is a hydrogen atom or an acyl group, or forms a single bond together with Z,

X is $–CH_2–$, –O– or –S–,

Z is $–OR^4$, $–NHCOR^5$, $–NHSO_2R^6$ or $–SR^7$, or forms a single bond together with R^2 or R^3,

each of R^4, R^5, R^6 and R^7 which are independent of one another, is a hydrogen atom, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, an aryl group or an aralkyl group,

and a dual line consisting of solid and broken lines is a single bond, a cis-double bond or a trans-double bond.

Ex. 1001, 31:2–26

12. A medicine containing 16-phenoxy-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$, 16-(3-chlorophenoxy)-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$, 16-phenoxy-15-deoxy-15,15-difluoro-13,14-dihydro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ or an alkyl ester or salt thereof as an active agent.

Id. at 32:22–27.

D. The Prior Art

Petitioner relies on the following prior art references:

Reference	Description	Date	Exhibit No.
Kishi	U.S. 5,292,754	Mar. 8, 1994	1005
Klimko	EP 0 639 563 A2	Feb. 22, 1995	1003
Ueno[1]	Japanese Unexamined Patent App. Pub. No. H7-70054	Mar. 14, 1995	1006

[1] Ueno is a Japanese patent application, and Petitioner provided an English-language translation as required by 37 C.F.R. § 42.63(b). Our citations are

Reference	Description	Date	Exhibit No.
Bezuglov 1982[2]	*Fluoroprostaglandins: A New Class of Bioactive Analogs of Natural Prostaglandins*, LIPIDS OF BIOLOGICAL MEMBRANES 88–91 (L. D. Bergelson, ed., 1982)	1982	1007
Bezuglov 1986	*Fluorodeoxy Prostaglandins, Synthesis and Perspectives*, PROSTAGLANDINS AND CARDIOVASCULAR DISEASES 191–200 (Takayuki Ozawa et. al. eds., 1986)	1986	1008

to that translation, which we assume for purposes of this Decision is accurate. Although the translation of Ueno is accompanied by a translator's certificate attesting to the accuracy of the translation (Ex. 1006, 67), the certificate is not an "affidavit" as required by 37 C.F.R. § 42.63(b) and as defined by 37 C.F.R. §§ 1.68 and 42.63(b). Specifically, the translator's certificate does not warn the translator "that willful false statements and the like are punishable by fine or imprisonment, or both." 37 C.F.R. § 1.68. *Petitioner must file, as a new exhibit, a satisfactory affidavit attesting to the accuracy of the translation within ten business days of this Decision.*

[2] Bezuglov 1982 is a Russian book chapter, and Petitioner provided an English-language translation as required by 37 C.F.R. § 42.63(b). Our citations are to that translation, which we assume for purposes of this Decision is accurate. As is the case with Ueno's translator's certificate, the translator's certificate accompanying Bezuglov 1982 (Ex. 1007, 11) is not an "affidavit" as required by 37 C.F.R. § 42.63(b) and as defined by 37 C.F.R. §§ 1.68 and 42.63(b). *Petitioner must file, as a new exhibit, a satisfactory affidavit attesting to the accuracy of the translation within ten business days of this Decision.*

E. The Asserted Grounds of Unpatentability

Petitioner challenges the patentability of claims 1–14 on the following grounds:

References	Basis	Challenged Claims
Klimko, Kishi, and Ueno	§ 103(a)	1–14
Klimko, Kishi, Bezuglov 1982 and/or Bezuglov 1986, and Ueno	§ 103(a)	1–14

II. ANALYSIS

A. Claim Interpretation

We interpret claims of an unexpired patent using the "broadest reasonable construction in light of the specification of the patent in which [the claims] appear[]." 37 C.F.R. § 42.100(b); *see Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). Only those terms in controversy need to be construed, and only to the extent necessary to resolve the controversy. *See Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999). For purposes of this Decision, based on the record before us, we determine that none of the claim terms requires an explicit construction.

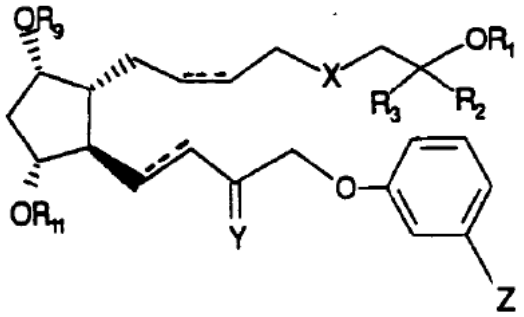
B. Obviousness over Klimko, Kishi, and Ueno

Petitioner contends that the subject matter of claims 1–14 would have been obvious over the combined teachings of Klimko, Kishi, and Ueno. Pet. 41–62. Petitioner relies on the Declaration of Mitchell A. deLong, Ph.D. ("deLong Declaration," Ex. 1027) and the Declaration of Aron D. Rose, M.D. ("Rose Declaration," Ex. 1028) in support of its contentions. *Id.*

1. Overview of Klimko

Klimko "relates to the use of cloprostenol, fluprostenol, their analogues and their pharmaceutically acceptable salts and esters to treat glaucoma and ocular hypertension." Ex. 1003, 2:3–5. Cloprostenol and fluprostenol "are synthetic analogues of $PGF_{2\alpha}$, a naturally-occurring F-series prostaglandin (PG)." *Id.* at 2:6–7. Klimko states that "[n]aturally-occurring prostaglandins are known to lower intraocular pressure (IOP) after topical ocular instillation, but generally cause inflammation, as well as surface irritation characterized by conjunctival hyperemia and edema," and that "[m]any synthetic prostaglandins have been observed to lower intraocular pressure, but such compounds also produce the aforementioned side effects." *Id.* at 2:50–54. Klimko teaches that "the addition of a chlorine atom or a trifluoromethyl group to the meta position on the phenoxy ring at the end of the omega chain provides a compound having excellent IOP reduction without the significant side effects found with other, closely related compounds." *Id.* at 3:50–53.

The compounds described in Klimko have the following general formula:



wherein R_1 is H, C_1–C_{12} straight-chain or branched alkyl, C_1–C_{12} straight-chain or branched acyl, C_3–C_8 cycloaklyl, a cationic salt moiety, or a

pharmaceutically acceptable amine moiety; R_2 and R_3 is H or C_1–C_5 straight-chain or branched alkyl, or R_2 and R_3 taken together may be O; X is O, S, or CH_2; R_9 is H, C_1–C_{10} straight-chain or branched alkyl, or C_1–C_{10} straight-chain or branched acyl; R_{11} is H, C_1–C_{10} straight-chain or branched alkyl, or C_1–C_{10} straight-chain or branched acyl; Y is O, or H and OR_{15}, wherein R_{15} is H, C_1–C_{10} straight-chain or branched alkyl, or C_1–C_{10} straight-chain or branched acyl; and Z is Cl or CF_3. *Id.* at 4:14–37. Klimko teaches that the preferred compounds include cloprostenol isopropyl ester, fluprostenol isopropyl ester, the 3-oxa form of cloprostenol isopropyl ester, 13,14-dihydrofloprostenol isopropyl ester, cloprostenol-1-ol, and 13,14-dihydrocloprostenol-1-ol pivaloate. Ex. 1003, 4:55–58.

Klimko reports studies comparing the IOP-lowering activity and side effects of five compounds: A) cloprostenol isopropyl ester; B) fluprostenol isopropyl ester; C) 16-phenoxy-17,18,19,20-tetranor $PGF_{2\alpha}$, isopropyl ester; D) 17-phenyl-18,19,20-trinor $PGF_{2\alpha}$, isopropyl ester; and E) 13,14-dihydro-17-phenyl-18,19,20-trinor $PGF_{2\alpha}$, isopropyl ester (known as latanoprost). *Id.* at 14:47–50; *see also id.* at 15, Tbl. 2 (showing the structures of compounds A–E). Tests of compounds A–E for hyperemia in guinea pigs show that compound C "produces significant hyperemia at low doses," compound D "produces less hyperemia than compound C, but significantly more than compound E . . ., which produces only mild hyperemia," and the hyperemia produced by compound A and compound B "appear to be intermediate between that of compound D and compound E, but this degree of hyperemia is also mild, and cannot be distinguished from that produced by compound E." *Id.* at 17:56–18:6. Compounds A–E were also tested for IOP-lowering effects in cynomolgus monkey eyes. *Id.* at 18:10–25. Based on these tests,

Klimko reports "that compounds A, B, C, and D produce similar degrees of IOP reduction with 0.3 µg doses," but that "compound E is essentially inactive at this dose." *Id.* at 19:29–30. Klimko further reports "that IOP reduction with 1 µg of compound A is greater than that produced by 0.3 µg of compound A, and the response to either of these doses of compound A is greater than the maximum reduction produced by either dose of compound E." *Id.* at 19:31–33. According to Klimko, these tests indicate compound A "is both more potent and produces a greater maximum response for IOP reduction than compound E." *Id.* at 19:33–35.

2. Overview of Kishi

Kishi "relates to the use of 15-deoxy-prostaglandin derivatives for the treatment of hypertension or glaucoma in the eyes." Ex. 1005, 1:15–17. Kishi states that "[t]he inventors of the invention have found new useful compounds by screening a large amount of prostaglandin derivatives which are stable and capable of being chemically synthesized," and also "found that derivatives of conventional prostaglandins which are derived from said conventional prostaglandins by deleting the hydroxy group at 15-position are more stable, particularly in the liquid phase, than the conventional prostaglandins, and that they show the intraocular pressure-reducing activity." *Id.* at 1:62–2:3. According to Kishi, the described 15-deoxyprostaglandins "have a significant intraocular pressure-reducing activity, while they do not produce any side effects such as hyperemia of conjunctiva, and initial increase in intraocular pressure which are often observed in known prostaglandins." *Id.* at 2:5–9.

3. Overview of Ueno

Ueno "relates to a new application for a 15-dehydroxy-prostaglandin compound, and to a specific new compound." Ex. 1006 ¶ 1. Ueno recognizes that "[i]t is known that a group of 15-dehydroxy-PG compounds that do not have a hydroxyl group at position 15 of a so-called natural PG has intraocular pressure reducing action," and that "15-dehydroxy-16-oxo PG compounds that do not have a hydroxyl group at position 15 and that have an oxo group at position 16 are effective for allergies, inflammation, and the like." *Id.* ¶ 7. Ueno then states that "the present inventors discovered that" the 15-dehydroxy-prostaglandin compounds that do not have a hydroxyl group or an oxo group at position 15 or position 16 "have superior antagonistic effect toward histamines, and therefore are useful for treating patients with allergies and inflammatory diseases." *Id.* ¶ 8.

Based on testing in guinea pigs, Ueno reports that 13,14-dihyrdro-15-dehydroxy-17,17-difluoro-PGE 1 methyl ester "has an antagonistic action against histamine, which is an inducer of allergic diseases and inflammatory diseases," and "is useful as an agent for treating allergic diseases, inflammatory diseases, and as a tracheal dilator." *Id.* ¶¶ 87–88. Ueno includes conjunctivitis, iritis, uveitis, and central retinitis as examples of inflammatory diseases. *Id.* ¶ 12.

4. Analysis

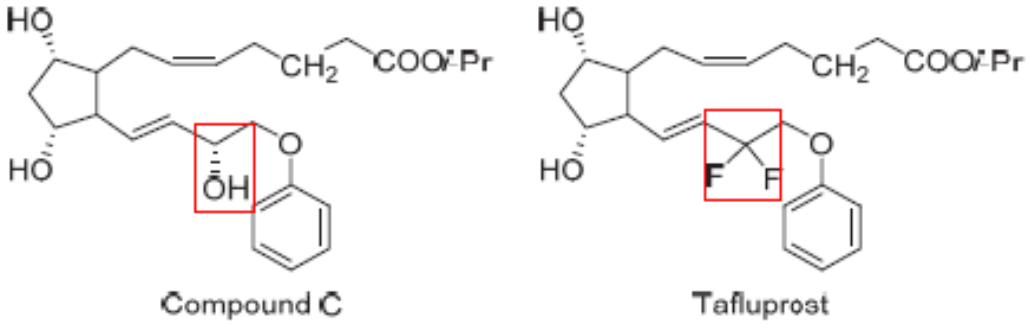
We generally follow a two-part inquiry to determine whether a new chemical compound would have been obvious over particular prior art compounds. *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1291–93 (Fed. Cir. 2012). First, we determine "whether a chemist of ordinary skill would have selected the asserted prior art compounds as lead compounds, or

starting points, for further development efforts." *Id.* at 1291. Second, we analyze whether there was a reason to modify a lead compound to make the claimed compound with a reasonable expectation of success. *Id.* at 1292.

A lead compound is defined as "a compound in the prior art that would be most promising to modify in order to improve upon its ... activity and obtain a compound with better activity." *Otsuka*, 678 F.3d at 1291 (alteration in original) (citing *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007)). Stated another way, "a lead compound is 'a natural choice for further development efforts.'" *Id.* (citing *Altana Pharma AG v. Teva Pharms. USA, Inc.*, 566 F.3d 999, 1008 (Fed. Cir. 2009)). Importantly, the analysis of whether a person of ordinary skill in the art would have chosen the prior art compound as a lead compound "is guided by evidence of the compound's pertinent properties," including "positive attributes such as activity and potency," "adverse effects such as toxicity," and "other relevant characteristics in evidence." *Id.* at 1292.

"Absent a reason or motivation based on such prior art evidence, mere structural similarity between a prior art compound and the claimed compound does not inform the lead compound selection." *Otsuka*, 678 F.3d at 1292; *see also Daiichi Sankyo Co., Ltd. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) ("[P]roviding a reason to select a compound as a lead compound depends on more than just structural similarity, but also knowledge in the art of the functional properties and limitations of the prior art compounds."). Establishing that a chemical compound would have been obvious over a structurally similar compound requires "a showing that the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention." *Takeda*, 492 F.3d at 1356.

Petitioner contends that it would have been obvious to start with Klimko's compound C as the "lead compound" and replace the hydroxyl group at the C-15 position with two fluorine (F) atoms to arrive at 16-phenoxy-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ ("tafluprost"), a compound that is specifically identified in dependent claim 3 and independent claim 12, and which falls within the scope of the generic formula of independent claim 1, of the '035 patent. The chemical structures of Klimko's compound C and tafluprost are shown side-by-side below:



Pet. 11. As indicated above, the only structural difference between the two compounds is the presence of a hydroxyl group versus two fluorine atoms at the C-15 position.

As support for its contention that a person having ordinary skill in the art would have selected Klimko's compound C as a lead compound, Petitioner cites to data presented in Klimko's Table 4 and Figure 2, which shows that compounds A–D "were found to exhibit significantly more IOP-reducing activity than the reference standard compound latanoprost that garnered FDA approval in June 1996." Pet. 46 (citing Ex. 1003, Example 6, Tbl. 4, Fig. 2; Ex. 1027 ¶ 61; Ex. 1028 ¶ 55). Although compound C shows more hyperemia than compounds A, B, D, and E (latanoprost), Petitioner cites Klimko's finding that "compound C showed longer-lasting efficacy

than the other compounds up through 6 hours after administration of the fifth dose" and also showed "the greatest percent IOP-reduction of all of the compounds at the first tabulated time point of 16 hours following administration of the fourth dose." *Id.* at 46–47 (citing Ex. 1003, 18:1–19:35; Ex. 1028 ¶¶ 56–59, 63); *see also* Ex. 1027 ¶ 108 (Dr. deLong testifying that a person having ordinary skill in the art would not have been dissuaded from selecting compound C based on the tests showing hyperemia in guinea pigs because compound C also demonstrated a long-lasting efficacy and the largest initial percent IOP reduction from baseline at 16 hours after administration of the fourth dose.).

Having selected Klimko's compound C as a lead compound that might benefit from modification, Petitioner contends that a person having ordinary skill in the art would have turned to Kishi's teaching that the hydroxyl at the C-15 position "is an underlying cause of the undesired hyperemia, and that removing the hydroxyl group at the C-15 position results in compounds that 'do not produce any side effects such as hyperemia.'" Pet. 50 (citing Ex. 1005, 1:65–2:11). Petitioner argues that a person having ordinary skill in the art "would also be aware from Kishi that removal of the hydroxyl group at the C-15 position of a $PGF_{2\alpha}$ isopropyl ester analogue like compound C could result in some loss of IOP-reducing activity," and, therefore, "would be further motivated to replace the C-15 hydroxyl group in compound C with a substituent other than hydrogen that could ameliorate any loss of IOP-reducing activity, with the reasonable expectation that the substitution would ameliorate or restore loss of IOP-reducing activity." *Id.* at 51.

According to Petitioner, a person having ordinary skill in the art would then consider Ueno's teachings "because it would have been known to one operating in the field at the time, but also because Ueno . . . specifically references Kishi." Pet. 51. Petitioner reasons that the combination of Kishi and Ueno teaches a person having ordinary skill in the art "to replace the hydroxyl group at the C-15 position of compound C disclosed in Klimko with two fluorine atoms in order to (1) eliminate the hyperemia associated with compound C, and (2) restore the IOP-reducing efficacy of compound C lost when the hydroxyl group is removed." *Id.* at 52 (citing Ex. 1027 ¶ 115).

Relying on the Declarations of Timothy L. Macdonald, Ph.D. ("Macdonald Declaration," Ex. 2001) and Robert D. Fechtner, M.D. ("Fechtner Declaration," Ex. 2002), Patent Owner challenges Petitioner's identification of Klimko's compound C as a lead compound meriting further study and modification. Prelim. Resp. 32–45. Patent Owner argues that Klimko teaches away from further development of compound C "because of its unfavorable IOP-lowering profile and intolerable side effects." *Id.* at 32–33. In particular, Patent Owner points to Klimko's identification of EP 364 417 A1 ("Stjernschantz," Ex. 2017), which Klimko says demonstrates that 16-phenoxy-17,18,19,20-tetranor $PGF_{2\alpha}$ isopropyl ester (which is compound (4) in Stjernschantz and Klimko's compound C) displays an initial increase in IOP followed by a decrease, and unacceptable hyperemia, and, therefore, displays an unacceptable therapeutic profile. *Id.* at 33–34 (citing Ex. 1003, 2:54–56, 3:38–44).

At this stage of the proceeding, Petitioner sets forth evidence in the deLong and Rose Declarations that Klimko's compound C potentially was a

useful medicine for reducing intraocular pressure and treating glaucoma and ocular hypertension with longer-lasting efficacy than other compounds tested in Klimko, and Patent Owner provides evidence in the Macdonald and Fechtner Declarations that Klimko's compound C had known drawbacks and that other prostaglandins were also promising. *See, e.g.*, Pet. 45–50; Ex. 1027 ¶¶ 57–71, 103–109; Ex. 1028 ¶¶ 52–63; Prelim. Resp. 32–45; Ex. 2001 ¶¶ 72–96; Ex. 2002 ¶¶ 24–41. This conflicting expert testimony creates a genuine issue of material fact as to whether Klimko's compound C would have been selected as a lead compound. For purposes of deciding whether to institute an *inter partes* review, we must view the facts in the light most favorable to Petitioner. *See* 37 C.F.R. § 42.108(c).

Patent Owner raises other arguments indicating potential flaws in Petitioner's lead compound analysis or disputing Petitioner's interpretation of the disclosures of the cited references. For example, Patent Owner argues that a person having ordinary skill in the art would not have been motivated: (1) to replace the C15 hydroxyl in compound C with a hydrogen to diminish side effects (based on Kishi) because doing so would reduce IOP-lowering activing; (2) to replace the C15 hydrogen with fluorine (based on Ueno) to restore the IOP-lowering activity lost when the hydrogen was substituted for the hydroxyl; and (3) to insert two fluorines at C15 (based on Ueno), "even though that difluoride bears little (if any) resemblance to the one hydroxyl that the modification is meant to mimic." Prelim. Resp. 5. Additionally, Patent Owner argues that Ueno is not directed to using fluorination to improve IOP-lowering activity, and a person having ordinary skill in the art "would not have formed a reasonable expectation of success of IOP-lowering based on prostaglandin activity in wholly different contexts." *Id.* at

48 (citing Ex. 2001 ¶ 100). We have considered these and the other arguments raised by Patent Owner, and although they cast some doubt on certain elements of Petitioner's lead compound analysis and create a genuine issue of material fact, we are persuaded, based on the current record, that Petitioner has established a reasonable likelihood of prevailing on its assertion that claims 1–14 would have been obvious over the combined teachings of Klimko, Kishi, and Ueno. The parties will have the opportunity to further develop these facts and arguments during trial, and the Board will evaluate the fully-developed record at the close of the evidence.

C. Obviousness over Klimko, Kishi, Bezuglov 1982 and/or Bezuglov 1986, and Ueno

Petitioner contends that the subject matter of claims 1–14 would have been obvious over the combined teachings of Klimko, Kishi, Bezuglov 1982 and/or Bezuglov 1986, and Ueno. Pet. 62–66. Petitioner relies on the deLong Declaration and the Rose Declaration in support of its contentions. *Id.*

1. Overview of Bezuglov 1982 and Bezuglov 1986

Bezuglov 1982 describes the synthesis and biological testing of 15-fluorine-15-deoxyfluoroprostaglandins. Ex. 1007, 88. Bezuglov 1982 teaches that "the replacement of the 15-hydroxyl group with fluorine protects the prostaglandin from the effects of 15-oxyprostaglandin dehydrogenase, which is a key enzyme in the metabolism of prostaglandins in the body." *Id.* Bezuglov 1982 reports the results of biological tests that show that the synthesized 15-fluoroprostaglandins A_2, $E_{2\alpha}$, F_2, and I_2 "did not lose the activity characteristic of prostaglandins" and "have prolonged activity compared to natural prostaglandins." *Id.* at 90. According to Bezuglov 1982, replacing the 15-hydroxyl group with fluorine can lead "to

the appearance of new properties in the analogs that were essentially absent in the corresponding natural prostaglandins." *Id.* at 91.

Bezuglov 1986 describes investigations of the synthesis and biological activity of fluorodeoxy prostaglandins. Ex. 1008, 191. In particular, Bezuglov 1986 focuses on the "substitution of the 15-hydroxyl group" because "biological deactivation of prostaglandins was induced by the action of 15-prostaglandin dehydrogenase." *Id.* at 199. Bezuglov 1986 reports that the substitution of fluorine for the hydroxyl group in prostaglandins at C15 "changed the character of their pharmacological action" and, in some cases, increase selectivity. *Id.* at 194. Bezuglov 1986 also reports that "[a]s expected, fluorination of prostaglandins in position 15 rendered them stable towards 15-prostaglandin dehydrogenase leading to prolonged activity of 15-fluorodeoxy prostaglandins upon intravenous injection in narcotized animals." *Id.*

2. Analysis

Petitioner relies on the same disclosures in Klimko, Kishi, and Ueno (and the arguments it made with respect to Petitioner's contention that the combination of Klimko, Kishi, and Ueno renders claims 1–14 obvious) to support its contention that the combination of Klimko, Kishi, Bezuglov 1982 and/or Bezuglov 1986, and Ueno teach or suggest all of the limitations of claims 1–14. Pet. 62. Petitioner additionally contends that a person having ordinary skill in the art "would be motivated in view of Bezuglov 1982 and/or Bezuglov 1986 to replace the hydroxyl group at the C-15 position" of Klimko's compound C "with a fluorine atom, with the reasonable expectation that this substitution would enhance and prolong the IOP-reducing activity" of compound C or, "at a minimum, restore any reduction

in IOP-reducing activity resulting from the removal of the hydroxyl group," and "because the exchange of fluorine for hydroxyl represents the most incremental change in structure that can be made." *Id.* at 64.

Patent Owner's arguments in response are generally the same as those made with respect to Petitioner's challenge based on Klimko, Kishi, and Ueno. For example, Patent Owner argues that "none of the Bezuglov 1982, Bezuglov 1986 and Ueno . . . references are directed to fluorination in the context of IOP-lowering," and a person having ordinary skill in the art "would not have formed a reasonable expectation of success of IOP-lowering based on prostaglandin activity in wholly different contexts." Prelim. Resp. 48. We already determined that Petitioner demonstrates a reasonable likelihood of showing that claims 1–14 would have been obvious over the combined teachings of Klimko, Kishi, and Ueno. *See supra* Section II.B. For the same reasons, we determine that Petitioner also demonstrates a reasonable likelihood of prevailing in showing that claims 1–14 would have been obvious over the combined teachings of Klimko, Kishi, Bezuglov 1982 and/or Bezuglov 1986, and Ueno.

III. CONCLUSION

Based on the arguments in the Petition and the Preliminary Response, and the evidence of record, we determine that Petitioner has demonstrated a reasonable likelihood that it would prevail on its challenge to claims 1–14 of the '035 patent.

IV. ORDER

In consideration of the foregoing, it is hereby

ORDERED that *inter partes* review is *granted* as to claims 1–14 of the '035 patent with respect to the following grounds:

Whether claims 1–14 are unpatentable under 35 U.S.C. § 103 as obvious over the combined teachings of Klimko, Kishi, and Ueno; and

Whether claims 1–14 are unpatentable under 35 U.S.C. § 103 as obvious over the combined teachings of Klimko, Kishi, Bezuglov 1982 and/or Bezuglov 1986, and Ueno;

FURTHER ORDERED that, pursuant to 35 U.S.C. § 315(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial commencing on the entry date of this Decision;

FURTHER ORDERED that Petitioner must file, as new exhibits, affidavits attesting to the accuracy of the translations of Ueno (Ex. 1006) and Bezuglov 1982 (Ex. 1007) that comply with 37 C.F.R. § 42.63(b) within ten business days of this Decision; and

FURTHER ORDERED that no ground other than those specifically granted above is authorized for *inter partes* review as to the claims of the '035 patent.

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