IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

ALLERGAN, INC.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	Civ. No. 09-333-SLR
	)	
BARR LABORATORIES, INC., TEVA PHARMACEUTICALS USA, Inc. TEVA PHARMACEUTICAL INDUSTRIES, LTD., and SANDOZ, INC.,	)	
	)	
Defendants.	)	

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OPINION

Dated: September 8, 2011
Wilmington, Delaware

ROBINSON, District Judge

I. INTRODUCTION

This action arises out of the filing of an Abbreviated New Drug Application ("ANDA")[1] by defendant Barr Laboratories, Inc. ("Barr") on March 26, 2009 for a generic version of Lumigan® (bimatoprost ophthalmic solution), used for the treatment of high eye pressure, also called intraocular pressure ("IOP"), in people with glaucoma or ocular hypertension. Plaintiff Allergan, Inc. ("Allergan") holds a New Drug Application ("NDA")[2] for Lumigan® 0.03% bimatoprost ophthalmic solution, and is the owner and assignee of the two Orange Book patents at issue in this case: U.S. Patent No. 5,688,819 ("the '819 patent") and U.S. Patent No. 6,403,649 ("the '649 patent"). In response to Barr's ANDA filing, which contained a paragraph IV certification as to the '819 and '649 patents, Allergan filed the instant patent infringement suit on May 7, 2009.[3] (D.I. 1) On July 2, 2010, the court granted Allergan's motion to amend the complaint to join defendants Teva Pharmaceuticals USA, Inc. ("Teva USA") and Teva Pharmaceutical Industries Ltd. ("Teva Ltd.") (collectively, "Teva").[4] On December 18, 2009, Allergan received notice of a paragraph IV certification filed by Sandoz, Inc.

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[1]No. 91-194.

[2]No. 21-275.

[3]*See* 35 U.S.C. § 271(e)(2)(A) ("(2) It shall be an act of infringement to submit – (A) an application under section 505(j) of the Federal Food, Drug, and Cosmetic Act or described in section 505(b)(2) of such Act for a drug claimed in a patent or the use of which is claimed in a patent[.]").

[4]Teva purchased Barr in 2008. Per the amended complaint, Barr is a wholly-owned subsidiary of Teva USA. (D.I. 93 at § 6) At trial, Teva stipulated to be bound by any judgment entered against Barr. (D.I. 211 at 445:9-18) The court hereinafter refers to Barr and Sandoz collectively as "defendants."

("Sandoz") that it had filed an ANDA[5] with the FDA for a generic version of Lumigan®. Allergan filed suit against Sandoz for infringement of the '819 and '649 patents,[6] which suit was consolidated with the action against Barr and Teva for purposes of trial. A bench trial on the issues of infringement and validity was held between January 31 and February 4, 2011. These issues have been fully briefed post-trial. The statutory 30-month stay against Barr expires on or about September 26, 2011.[7] The stay against Sandoz expires on or about June 18, 2012. The court has jurisdiction pursuant to 28 U.S.C. §§ 1331, 1338(a) and 1400(b). Having considered the documentary evidence and testimony, the court makes the following findings of fact and conclusions of law pursuant to Fed. R. Civ. P. 52(a).

II. FINDINGS OF FACT AND CONCLUSIONS OF LAW

A. The Technology at Issue

1. Glaucoma and ocular hypertension

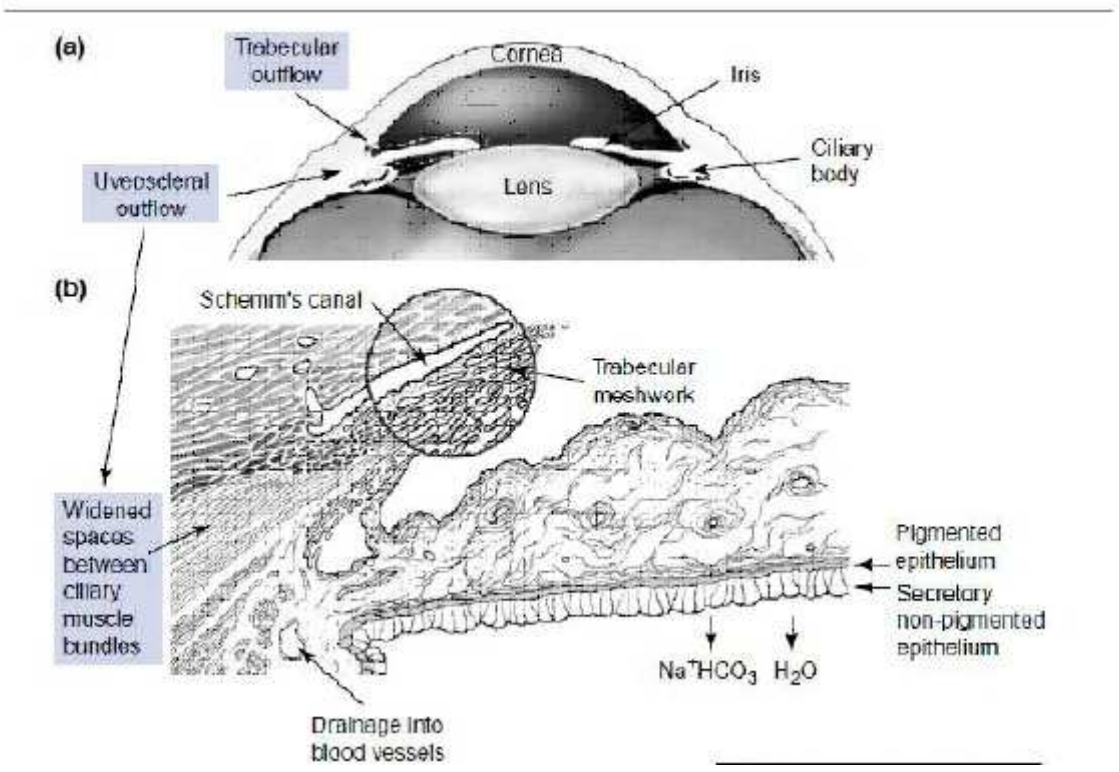
1. Glaucoma is a disease of the eye in which the cells and nerve fibers that take vision from the back of the eye to the brain are damaged and die. (D.I. 210 at 70:2-4) The major risk factor for glaucoma has been identified as "ocular hypertension" or high IOP. (*Id.* at 70:4-7; '819 patent, col. 1:39-40) IOP is maintained by aqueous humor, which is fluid between the cornea and the lens. (D.I. 211 at 460:14-17) Aqueous

[5]No. 200487.

[6]Civ. No. 10-024-SLR.

[7]Barr asserts that the stay expires on September 26, 2011, while Allergan represents that the stay expires September 29, 2011. The court utilizes the most conservative date.

humor is continuously produced and flows from the ciliary body to the front of the eye. It exits through one of two pathways, called the trabecular meshwork and the uveoscleral outflow pathway. The traditional pathway by which the aqueous humor leaves the eye is the trabecular meshwork pathway through the Schlemm's canal, which is between the iris (colored part of the eye) and the cornea. (D.I. 210 at 75:8-12, D.I. 211 at 462:12-21) The uveoscleral pathway is the alternative or additional pathway, which is between the sclera and the ciliary body. (*Id.* at 462:12-21; 464:18-21) These pathways are shown generally in the diagram below.[8]

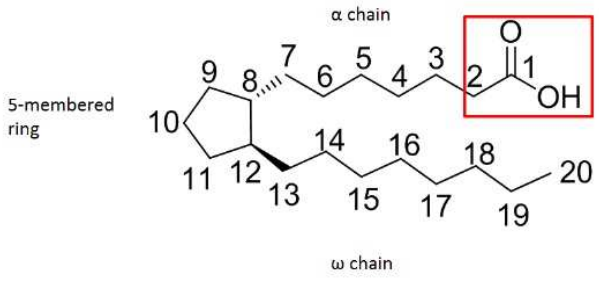


[8]The parties do not cite to an admitted exhibit (rather than a trial demonstrative) reflecting the general anatomy of the eye. The court utilizes a diagram provided in the post-trial papers for informational purposes only.

Through this constant flow, the aqueous humor brings nourishment – vitamins, sugars, and amino acids – to the cornea. (*Id.* at 460:21-461:14) Too much aqueous humor, however, disturbs the IOP and is a major risk factor for the development of glaucoma. (*Id.* at 462:6-14) As described in the patents in suit, "increased intraocular tension is due to the obstruction of aqueous humor outflow." ('819 patent, col. 1:48-49)

2. Several different types of medications are utilized to treat glaucoma because of variable tolerability and effectiveness from patient to patient. (D.I. 210 at 70:22-71:11) The active ingredient in Lumigan® is bimatoprost, which acts to decrease IOP in the eye by increasing the flow of aqueous humor leaving the eye. (D.I. 210 at 71:9-13; D.I. 211 at 462:15-18) "Bimatoprost is a prostamide, a synthetic structural analog of prostaglandin with ocular hypotensive activity" that "selectively mimics the effects" of prostamides by increasing outflow of aqueous humor. (PTX-342)

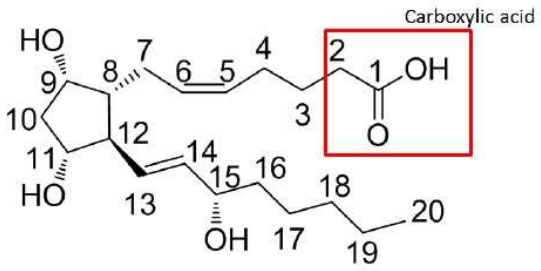
3. A discussion of bimatoprost is best framed by a background of prostaglandins. Prostaglandins are a class of naturally-occurring substances that share the following twenty-carbon structure (D.I. 210 at 132:9-16):



(D.I. 216 at 6) In the above diagram, the carbon atoms are numbered from 1 to 20. Carbon atoms numbered 1 through 7, taken together, form what is known as the α (alpha) chain. Carbon atoms numbered 13 through 20, taken together, form what is

known as the ω (omega) chain. Carbon atoms 8 through 12 form a five-membered (cyclopentane) ring. In addition to these features, all naturally-occurring prostaglandins share a specific feature at the first carbon: a carboxylic acid (C1 carboxylic acid), highlighted above. (D.I. 210 at 132:14-16; 132:24-133:5)

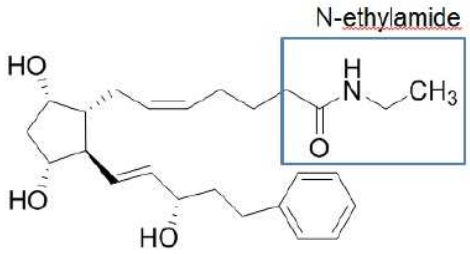
4. Prior to the inventions at issue, a naturally-occurring prostaglandin ($PGF_{2\alpha}$) was a known hypotensive agent, that is, $PGF_{2\alpha}$ was known to lower IOP by increasing the outflow of fluid. (D.I. 216 at 6; DTX-995; DTX-991; '819 patent, col. 2:11-13 & col. 2:20) The structure of $PGF_{2\alpha}$ is depicted below.



(D.I. 216 at 7) While $PGF_{2\alpha}$ shares the 20-carbon backbone and C1 carboxylic acid of naturally occuring prostaglandins, it has several distinct features that differentiate it from other prostaglandins: (1) a double bond between C5 and C6; (2) a double bond between C13 and C14; and (3) hydroxyl groups (-OH) at C9, C11, and C15, each in a specific configuration. (D.I. 210 at 134:14-135:16) More specifically, carbons C4 and C7 are on the same side of the double bond (the "cis position"), while carbons C13 and C14 are on opposite sides of the double bond (the "trans position") in 3D space. (*Id.*) The hydroxyl groups all point in the same direction (as depicted above, away from the reference plane). (*Id.*)

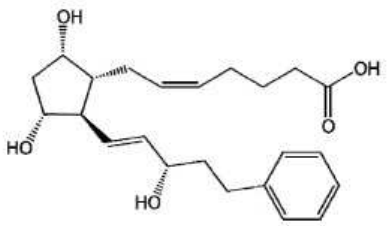
5. Bimatoprost ((Z-7-[(1R,2R, 3R, 5S)-3,5-Dihydroxy-2-[1E,3S)-3-hydroxy-5-

phenyl-1-pentenyl]cyclo-pentyl]-5-N-ethylheptenamide) has the structure depicted below.



(PTX-342; D.I. 216 at 19) Bimatoprost belongs to a class of compounds called "prostamides," and is also called 17-phenyl $PGF_{2\alpha}$ C1 ethylamide. As this name implies, bimatoprost is $PGF_{2\alpha}$ having a phenyl ring at C17 and an ethylamide at the C1 position. Lumigan® contains 0.03% (or 0.3mg/mL) of bimatoprost in solution. (PTX-342)

6. Bimatoprost's mechanism of action is greatly debated in this case. According to defendants, bimatoprost is a "prodrug," or a compound that has no biological activity itself, but is converted to an active drug (bimatoprost free acid) once in the body. (D.I. 210 at 136:4-8; D.I. 212 at 675:25-676:4) More specifically, defendants assert that bimatoprost is an amide prodrug administered to deliver bimatoprost free acid (or 17-phenyl $PGF_{2\alpha}$) to the body. Bimatoprost free acid has a phenyl ring at C17 and a carboxylic acid at the C1 position, as depicted below.



Defendants assert that bimatoprost undergoes hydrolysis[9] and converts to bimatoprost free acid, when bimatoprost comes into contact with water and amidases enzymes in the eye. (D.I. 211 at 491:9-492:9; 492:22-493:8) The resultant bimatoprost free acid activates the prostaglandin FP receptor. (D.I. 212 at 595:19-25)

7. While Allergan's witnesses confirmed that at least a "very low" level of bimatoprost hydrolizes in the eye (D.I. 210 at 101:23-102:3; D.I. 211 at 359:20-23; 669:5-19; 689:19-25; D.I. 213 at 921:5-8), it asserts that bimatoprost resists conversion to the C1 carboxlyic acid and lowers IOP in the eye directly. (D.I. 210 at 254:23-255:2; D.I. 212 at 669:23-25; D.I. 213 at 907:1-16; 1109:9-11 ("Prodrugs need to be released at an adequate rate in sufficient amounts to produce the active agent. If it's too slow, it will not do that.") That is, **intact** bimatoprost lowers IOP, and bimatoprost is not a prodrug. Allergan presented evidence that its scientists initially synthesized $PGF_{2\alpha}$ dimethylamide and $PGF_{2\alpha}$ monomethylamide – compounds lacking a C1 carboxylic acid and also lacking the 17-phenyl ring of bimatoprost – as potential FP receptor antagonists[10] to be used in evaluating $PGF_{2\alpha}$-related agonist compounds under development. (D.I. 210 at 142:4-146:24) Allergan thereafter discovered that the two $PGF_{2\alpha}$ C1 amide compounds lowered IOP through another, previously unknown receptor: the "nonclassical FP receptor." (*Id.*, D.I. 210 at 188:9-189:6; 252:10-254:11; PTX-119) Allergan's $PGF_{2\alpha}$-analog program led to the synthesis of bimatoprost on

[9]Generally, a reaction of a compound with water that results in the decomposition of that compound.

[10]The function of an antagonist is to bind to a receptor and block the effects of an agonist (and, therefore, also block the agonist's biological response). (140:3-14, 171:13-17; 211:1-4)

February 3, 1992.[11] (D.I. 210 at 156:12-157:9; PTX-391 at AGN-BAR-02132270) In short, Allergan asserts that bimatoprost lowers IOP directly through a novel FP receptor, while defendants argue that bimatoprost is a prodrug that hydrolyzes to bimatoprost free acid, which then works on the classical FP receptor.

2. Patents-in-suit

8. The '819 and '649 patents describe and claim bimatoprost and methods of using bimatoprost to treat ocular hypertension or glaucoma. Bimatoprost was described in an application filed by Allergan on September 21, 1992 that issued as U.S. Patent No. 5,352,708 ("the '708 patent"). (D.I. 210 at 159:5-161:20) The '708 patent does not claim bimatoprost, rather, it claims "a variety of esters and amides of the primary [$PGF_{2\alpha}$] alcohol and prodrugs of the other hydroxyl groups on the ring." (*Id.* at 159:21-160:8)

9. The '819 patent was filed on February 22, 1996 and issued November 18, 1997. The '819 patent is related to the '708 patent, to which it claims priority. Notably, the '819 patent incorporates by reference the specification of the '708 patent as well as the other patents in the chain. ('819 patent, col. 1:7-15) The '619 patent followed in the chain of continuation applications claiming priority to the '819 patent; it was filed March 6, 2000 and issued June 11, 2002. As a continuation, the '619 patent shares the same specification as the '819 patent, and also incorporates the '708 patent by reference. ('619 patent, col. 1:7-18)

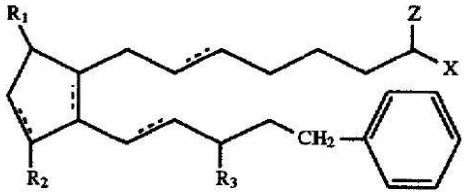
10. The patents-in-suit disclose that particular prostaglandins, such as $PGF_{2\alpha}$,

[11]Defendants' expert conceded that inventor Steven W. Andrews ("Andrews") was the first bench chemist to synthesize bimatoprost. (D.I. 212 at 588:14-22)

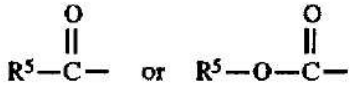
"are highly effective ocular hypotensive agents and are ideally suited for the long-term medical management of glaucoma." ('819 patent, col. 2:12-15 & col. 2:20) The isopropyl ester of $PGF_{2\alpha}$ has significantly greater hypotensive potency than $PGF_{2\alpha}$. (*Id.*, col. 2:34-37) Prostaglandins have been associated with "ocular surface (conjunctival) hyperemia" (red eye) and "foreign-body sensation ha[s] been consistently associated with the topical ocular use of such compounds, in particular $PGF_{2\alpha}$ and its prodrugs." (*Id.*, col. 2:41-46) The clinical potential of glaucoma with prostaglandins has been "greatly limited by these side effects." (*Id.*, col. 2:46-49) The inventors provided that the disclosed cyclopentane heptanoic acids – 2-cycloalkyl or arylalkyl compounds and derivatives thereof wherein the carboxylic acid group is replaced by a non-acid substituent – have shown "pronounced effects on smooth muscle and are potent ocular hypotensive agents." Further, "in the case of glaucoma surprisingly, [they] cause no or significantly lower ocular surface hyperemia than the parent compounds." (*Id.*, col. 3:9-18) Put most simply, substitution of the carboxylic acid group worked just as well, and irritated the eye less.

11. Allergan alleges that defendants infringe claim 10 of the '819 patent. (D.I. 216 at 31 & n.15) Claim 10 depends from claim 9, which further depends from claim 8, et cetera to independent claim 5. These claims provide as follows.

5. A method of treating ocular hypertension or glaucoma which comprises applying to the eye an amount sufficient to treat ocular hypertension or glaucoma of the formula

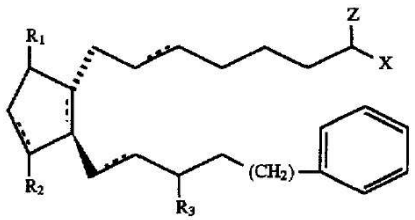


wherein the dashed bonds represent a single or double bond which can be in the cis or trans configuration, X is a radical selected from the group consisting of $–OR^4$ and $–N(R^4)_2$ wherein R^4 is selected from the group consisting [of] hydrogen, a lower alkyl radical having from one to six carbon atoms,



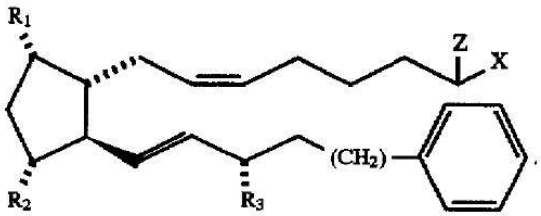
wherein R^5 is a lower alkyl radical having from one to six carbon atoms; Z is =O or represents 2 hydrogen radicals; R_3 is =O , –OH or – $O(CO)R_6$; one of R_1 and R_2 is =O, –OH or a $–O(CO)R_6$ group, and the other one is – OH or $–O(CO)R_6$, or R_1 is =O and R_2 is H, wherein R_6 is a saturated or unsaturated acyclic hydrocarbon group having from 1 to about 20 carbon atoms, or $–(CH_2)_mR_7$ wherein m is 0-10, and R_7 is cycloalkyl radical, having from three to seven carbon atoms, or a hydrocarbyl aryl or heteroaryl radical having from four to ten carbon atoms wherein the heteroatom is selected from the group consisting of nitrogen, oxygen and sulfur atoms; or a pharmaceutically-acceptable salt thereof, provided however that when Z is =O, then X is not $–OR^4$.

6. The method of claim 5 wherein said compound is represented by the formula

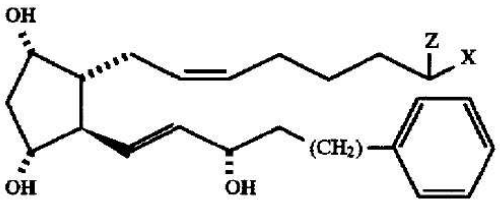


wherein hatched lines indicate the α configuration and solid triangles indicate the β configuration.

7. The method of claim 6 wherein said compound is represented by the formula



8. The method of claim 7 wherein said compound is represented by the formula



and the 9- and/or 11- and/or 15 esters, thereof.

9. The method of claim 8 wherein Z is =O and X is $-N(R^4)_2$.

10. The method of claim 9 wherein said compound is selected from the group consisting of

cyclopentane heptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3,5-dihydroxy, $[1_\alpha,2_\beta,3_\alpha,5_\alpha]$;

cyclopentane N,N-dimethylheptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy,$[1_\alpha,2_\beta,3_\alpha,5_\alpha]$;

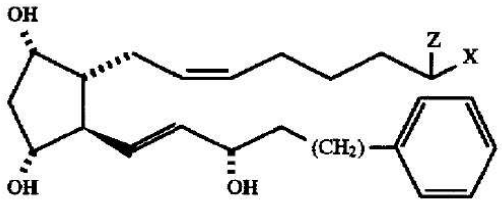
cyclopentane N-isopropyl heptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, $[1_\alpha,2_\beta,3_\alpha,5_\alpha]$;

cyclopentane N-ethyl heptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, $[1_\alpha,2_\beta,3_\alpha,5_\alpha]$; and

cyclopentane N-methyl heptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, $[1_\alpha,2_\beta,3_\alpha,5_\alpha]$.

Therefore, claim 10 recites a method of treating ocular hypertension or glaucoma which

comprises applying to the eye in an amount sufficient to treat ocular hypertension or glaucoma one of the five compounds listed above, and having the formula (of claim 8)



wherein Z is =O and X is $-N(R^4)_2$.

12. Allergan asserts that defendants infringe claims 1-3 of the '649 patent (D.I. 216 at 28 & n.13), which claims read as follows.

> 1. A compound, that is cyclopentane N-ethyl heptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3,5-dihydroxy, $[1_\alpha,2_\beta,3_\alpha,5_\alpha]$).
>
> 2. A method of treating ocular hypertension which comprises applying to the eye an amount sufficient to treat ocular hypertension of the compound of claim 1.
>
> 3. A method of treating glaucoma which comprises applying to the eye an amount sufficient to treat glaucoma of the compound of claim 1.

B. Claim Construction

1. Standards

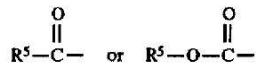
13. Claim construction is a matter of law. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1330 (Fed. Cir. 2005) (en banc). Claim construction focuses on intrinsic evidence - the claims, specification and prosecution history - because intrinsic evidence is "the most significant source of the legally operative meaning of disputed claim language." *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996); *Markman v. Westview Instruments, Inc.,* 52 F.3d 967, 979 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S.

370 (1996). Claims must be interpreted from the perspective of one of ordinary skill in the relevant art at the time of the invention. *Phillips*, 415 F.3d at 1313.

14. Claim construction starts with the claims, *id.* at 1312, and remains centered on the words of the claims throughout. *Interactive Gift Express, Inc. v. Compuserve, Inc.*, 256 F.3d 1323, 1331 (Fed. Cir. 2001). In the absence of an express intent to impart different meaning to claim terms, the terms are presumed to have their ordinary meaning. *Id.* Claims, however, must be read in view of the specification and prosecution history. Indeed, the specification is often "the single best guide to the meaning of a disputed term." *Phillips*, 415 F.3d at 1315.

2. Issue at bar

15. There is no claim construction dispute with respect to the '649 patent. The parties agree that the limitations of the '819 patent claims should be given their ordinary meanings, with one exception: the parties dispute whether the two R^4 elements contained in the " $-N(R^4)_2$" limitation need be identical. (D.I. 143) The claims further contain a Markush group, requiring that "R^4 is selected from the group consisting of hydrogen, a lower alkyl radical having one to six carbon atoms, or



wherein R^5 is a lower alkyl radical having from one to six carbon atoms."

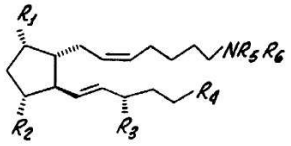
3. Discussion

16. For the reasons discussed *infra*, the court construes the disputed claim language consistent with the tenets of claim construction set forth above as follows:

"**–N(R^4)$_2$**" does not require that the two R^4 elements are identical.

a. Plain language

17. At the forefront, the court agrees with defendants that the plain and ordinary meaning of –N(R^4)$_2$ would support its construction that the R^4 elements are identical functional groups. The $(X)_y$ nomenclature is commonly used to designate repeating substituents, for example, in a polymer chain. Extrinsic evidence introduced by defendants demonstrates that differing substituents are commonly given unique designations, for example, R' and R". (D.I. 155, ex. C) In another Allergan patent with one common inventor to the '819 patent,[12] the designation "R_5R_6NH" was used to denote the functional groups present in similar compounds, as follows.



(U.S. Patent No. 5,545,665, fig. 2 (cited at D.I. 155 at 9))

18. This does not end the inquiry, however. "Although words in a claim are generally given their ordinary and customary meaning, a patentee may choose to be his own lexicographer and use terms other than their ordinary meaning, as long as the special definition of the term is clearly stated in the patent specification or file history." *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). Allergan argues that the intrinsic record supports its argument that the inventors chose to use –N(R^4)$_2$ in a manner inconsistent with its ordinary meaning. The court turns, then, to

[12]Inventor Robert M. Burk ("Burk").

the intrinsic record.

b. The intrinsic evidence

19. Allergan argues that the use of the $–N(R^4)_2$ limitation in the claims supports its construction. While two of the compounds recited in dependent claim 10 have identical R^4 elements, three compounds do not – including bimatoprost (cyclopentane N-**ethyl** heptenamide-5-cis-2- (3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, $[1_\alpha,2_\beta,3_\alpha,5_\alpha]$), which has an amide group at the C1 position ($R–O{=}C–NH–CH_2CH_3$). That is, bimatoprost has two different groups at the R^4 position, each of which is named in the Markush group: hydrogen (H) and an ethyl group (CH_2CH_3). Similarly, claim 10 also includes cyclopentane N-**isopropyl** heptenamide-5-cis-2- (3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, $[1_\alpha,2_\beta,3_\alpha,5_\alpha]$ and cyclopentane N-**methyl** heptenamide-5-cis-2- (3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, $[1_\alpha,2_\beta,3_\alpha,5_\alpha]$, containing different R^4 groups (hydrogen (H) and isopropyl ($CH_3–CH–CH_3$) or methyl (CH_3) groups, respectively). If claim 10 further narrows independent claim 5, the $–N(R^4)_2$ term cannot be construed to require identical R^4 groups.

20. Consistent with the foregoing, claim 18, which depends further from claim 11, also recites three compounds where X is $–N(R^4)_2$ and the two R^4 elements differ: (1) bimatoprost; (2) cyclopentane N-**isopropyl** heptenamide-5-cis-2- (3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, $[1_\alpha,2_\beta,3_\alpha,5_\alpha]$; and (3) cyclopentane N-**methyl** heptenamide-5-cis-2- (3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, $[1_\alpha,2_\beta,3_\alpha,5_\alpha]$. The claims consistently include differing R^4 groups within the

context of the "–$N(R^4)_2$" term.

21. The specification contains a comparable disclosure. It identifies "novel compounds [that] may be used in the pharmaceutical compositions and the methods of treatment of the present invention" as including: (1) bimatoprost (cyclopentane N-**ethyl** heptenamide-5-cis-2- (3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1_α,2_β,3_α,5_α]); (2) cyclopentane N-**isopropyl** heptenamide-5-cis-2- (3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1_α,2_β,3_α,5_α]; and (3) cyclopentane N-**methyl** heptenamide-5-cis-2- (3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1_α,2_β,3_α,5_α]. These same three compounds are recited in asserted claim 10 (and non-asserted claim 18). ('819 patent, col. 7:19-21, col. 7:41-49)

22. The '819 patent's file wrapper also generally supports Allergan's interpretation. Following the issuance of the '819 patent, Allergan submitted an Application for Extension of Patent Term Under 35 U.S.C. § 156 based on the FDA's regulatory review with respect to Lumigan®. (D.I. 163 at JA-134-40) Allergan represented in its submission that the '819 patent "claims the active ingredient of Lumigan®, bimatoprost[.]" (*Id.* at JA-137) The PTO thereafter issued its Notice of Final Determination approving a patent term extension (of 698 days) for the '819 patent, noting that the '819 patent "claims the method of use of the human drug product Lumigan® (bimatoprost)." (*Id.* at JA-298) Although, as defendants point out, these characterizations of the claims did not occur in the context of overcoming prior art rejections, the court discerns no reason to completely discount their persuasiveness.

23. Relatedly, defendants do not point to any intrinsic evidence contradicting

Allergan's construction, for example, a clear disclaimer or disavowal of claim scope. (D.I. 155 at 6-8) Defendants focus on the fact that the inventors utilized different variables to denote different substituents elsewhere in claim 5, for example, by using R_1 to R_7, respectively. (*Id.*) Thus, defendants argue, the inventors would have chosen different labels for R^4, such as R^4 and $R^{4'}$, had they intended on claiming two different R^4 groups. (*Id.*) *See, gen., Symantec Corp. v. Computer Associates Intern.*, 522 F.3d 1279, 1289 (Fed. Cir. 2008) ("the general assumption is that different terms have different meanings").

c. Conclusion

24. In view of the foregoing, it is the court's conclusion that the inventors overcame the "heavy presumption"[13] that the ordinary meaning of $(R^4)_2$ does not apply by clearly manifesting, through their use of the term $-N(R^4)_2$ in the claims and their description of the invention in the specification, their intent for $(R^4)_2$ to encompass substituents with different R^4 groups, such as bimatoprost.[14] *See Laryngeal Mask Co. Ltd v. Ambu*, 618 F.3d 1367, 1372 (Fed. Cir. 2010) (suggesting that a "special definition" is preferred, but that the lexicographer rule applies where the specification "clearly indicate[s] the patentee's intent" to give a unique meaning to the term) (citing, *inter alia*, *Helsderfer v. Bobrick Washroom Equip., Inc.*, 527 F.3d 1379, 1383 (Fed. Cir.

[13] *See, e.g., Housey Pharmaceuticals, Inc. v. Astrazeneca UK Ltd.*, 366 F.3d 1348, 1352 (Fed. Cir. 2004) ("When construing patent claims, there is a heavy presumption that the language in the claim carries its ordinary and customary meaning amongst artisans of ordinary skill in the relevant art at the time of the invention.").

[14] The court denies as moot Allergan's motion to exclude the declaration of defendants' expert Douglass Taber on the basis of delay, which declaration spoke to the common understanding of $(R^4)_2$. (D.I. 178)

2008)). The inventors were free to act as their own lexicographers, and defendants do not point to any intrinsic evidence clearly limiting the scope of $–N(R^4)_2$. Insofar as Allergan's construction preserves the validity of the dependant claims, and is not contradicted by the intrinsic record, the court declines to limit R^4 to identical groups.[15] *See Frank's Casing Crew & Rental Tools, Inc. v. Weatherford Int'l, Inc.*, 389 F.3d 1370, 1377 (Fed. Cir. 2004) ("If possible, this court construes claim terms in a manner that renders the patent internally consistent.") (citation and internal quotations omitted); *see also, e.g., Oatey Co. v. IPS Corp.*, 514 F.3d 1271, 1276-77 (Fed. Cir. 2008) ("We normally do not interpret claims in a way that excludes embodiments disclosed in the specification" absent a clear disclaimer) (citations omitted).

C. Infringement

25. At trial, defendants did not dispute that their ANDA products literally infringe claims 1-3 of the '649 patent. (D.I. 210 at 39:12-40:6) Post-trial, defendants concede infringement of the '819 patent under Allergan's claim construction. (D.I. 219 at 2)

26. Notwithstanding defendants' concessions, insofar as Allergan bears the burden of proof on infringement, the court will briefly recite Allergan's infringement evidence adduced at trial. Infringement of the '649 patent is straightforward. Claim 1 of the '649 patent claims bimatoprost, the active ingredient in Barr's and Sandoz's ANDA product. (D.I. 211 at 411:13-412:8) Claim 2 of the '649 patent recites a method of treating ocular hypertension comprising applying bimatoprost. Allergan's expert, Dr.

[15]Having so construed the term, the court dismisses defendants' argument that claim 10 of the '819 patent is invalid under 35 U.S.C. § 112, ¶ 4 under defendants' proposed construction. (D.I. 217 at 59-60)

Timothy L. Macdonald ("Macdonald"), testified that defendants' ANDA products are indicated for this purpose and, therefore, defendants indirectly infringe claim 2. (*Id.* at 417:13-419:16; *see also* PTX-564 at Barr_Bimat000021; PTX-792 at SAND-BIMA001519, -523) Similarly, Macdonald testified that defendants' ANDA products are also indicated for the treatment of glaucoma and, therefore, defendants indirectly infringe claim 3 of the '649 patent, directed to a method of treating that condition. (D.I. 211 at 419:21-420:6)

27. Macdonald also explained at trial that bimatoprost satisfies all of the limitations of claims 5-9 of the '819 patent (including the "X is $-N(R^4)_2$" limitation) and infringes claim 10 of the '819 patent under Allergan's construction of the $-N(R^4)_2$ term. (*Id.* at 424:7-429:6) The claims are drawn to a method of treating ocular hypertension or glaucoma with a compound such as bimatoprost and, as cited above, defendants' literature demonstrates that their ANDA products are indicated for both purposes.

28. As defendants do not cite any contrary evidence of noninfringement (D.I. 219 at 2, 28-36), the court finds Allergan has met its burden of proof on infringement.

D. Validity

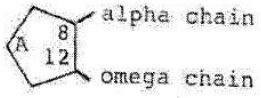
Defendants assert that the '649 and '819 patents are invalid under both inherent anticipation and obviousness theories. The court's discussion is best framed by an overview of the primary invalidity reference asserted at trial – a patent to Johan Stjernschantz, published as PCT application no. WO 90/02253 on March 22, 1990 (hereinafter, "Stjernschantz"). (DTX-882) The court will then discuss defendants' expert's opinion and assertions post-trial.

1. Stjernschantz

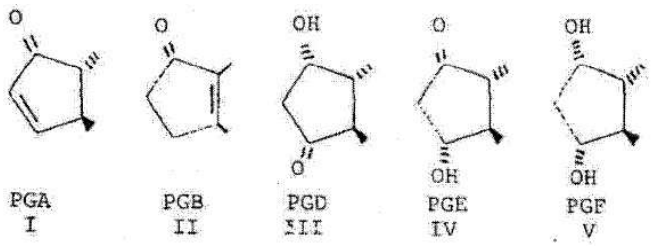
29. Stjernschantz is entitled “Prostaglandin Derivatives for the Treatment of Glaucoma or Ocular Hypertension,” and “relates to opthamological compositions for topical treatment of [these conditions] comprising an effective intraocular pressure reducing derivative of PGA, PGB, PGD, PGE or PGF in which the omega chain contains a ring structure, in an opthamologically compatible carrier.” (DTX-822, title, abstract) Stjernschantz also provides for methods of preparation of said compositions and their use in the treatment of glaucoma and ocular hypertension. (*Id*., abstract)

30. Stjernschantz provides that prostaglandins “have met an increasing interest as IOP-lowering substances” and that, while they may “cause an increase in the uveoscleral outflow, . . . they do not appear, however, to have any effect on the formation of aqueous humor or to the conventional outflow through Schlenn’s canal.” (*Id.* at 3) A “limiting factor” on the use of prostaglandins and their derivatives for treating glaucoma or ocular hypertension “is their property of causing superficial irritation and vasodilation in the conjunctiva,” as well as a possible “irritant effect on the sensory nerves of the cornea.” (*Id.*) Stjernschantz provides that a solution to these problems is “the use of certain derivatives of prostaglandins A, B, D, E and F, in which the omega chain has been modified with the common feature of containing a ring structure[.]” (*Id.* at 4)

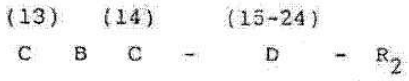
31. Stjernschantz’s prostaglandin derivatives have the following structure.



(*Id.*) In derivatives PGA, PGB, PGD, PGE and PGF, "A" has the following formula.

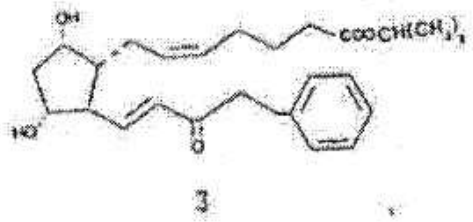


(*Id.*) The omega chain is defined by the following formula.



The "C"s above represent carbon at the designated number, the "B" is a single, double or triple bond, "D" is a chain with "the substituent on C-15 preferably being a carbonyl group, [ ] (R)-OH or (S)-OH," and R_2 is a ring structure. (*Id.* at 5)

32. Stjernschantz states that, to achieve the "unique property of causing insignificant side effects while retaining the intraocular pressure lowering effect," "the crucial modification of the molecule is a ring structure at the omega chain." (*Id.* at 22) The "most preferred derivatives at present" were disclosed as "those in which the omega chain of the prostaglandin has the 18,19,20-trinor form, and especially the 17-phenyl analogs, such as the 15-(R)-, 15-dehydro and 13,14-dihydro-17-phenyl-18,19,20-trinor forms," as depicted below (representing compounds 3, 6, 7 and 9 of the invention, respectively).



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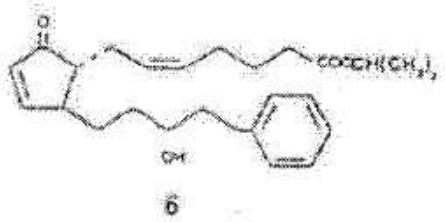

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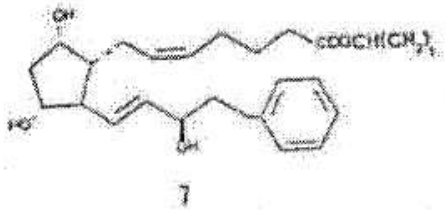

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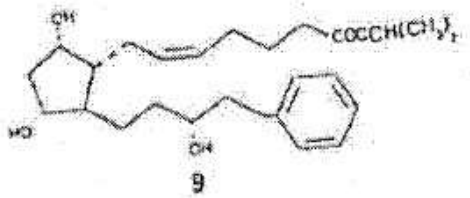


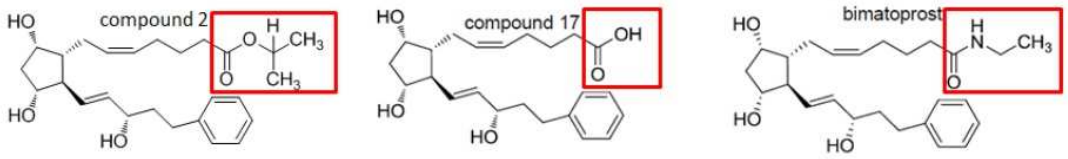
9

(*Id.* at 6, 23) Compound 9 became "latanoprost" which is marketed as "Xalatan®," a leading antiglaucoma treatment (outselling Lumigan®). (D.I. 213 at 1008:10-15; PTX-994) Compound 9 has a single bond between C13 and C14.

33. Defendants focus on two other embodiments disclosed in Stjernschantz – compounds 2 and 17. Compound 17 is bimatoprost free acid, or 17-phenyl $PGF_{2\alpha}$, characterized by a carboxylic acid functional group (– COOH) at C1. Compound 2 is an isopropyl ester that converts into bimatoprost upon hydrolysis.[16] It is defendants'

[16]Compound 2 is identical in structure to compound 9 (latanoprost) except that compound 2 has a double bond between C13 and C14. Latanoprost converts into

position that compound 2 renders the claims at issue invalid. The structural difference between compound 17 (bimatoprost free acid) and bimatoprost is, again, the functional group at the C1 position: bimatoprost has an ethyl amine. The following is an illustrative comparison between compounds 2, 17 and bimatoprost, with their respective isopropyl ester, carboxylic acid, and ethyl amine functional groups highlighted, respectively.



(D.I. 220 at 21)

34. Stjernschantz Table II discloses bimatoprost free acid (compound 17) in the context of describing the reactions utilized in two other compounds of the invention (compounds 7 and 2). That is, compound 17 is an intermediate in the process of achieving 17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester (compound 2) and 15-(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester (compound 7). (DTX-822 at 24)

2. Inherent anticipation

The court turns first to defendants' post trial argument that the claims in suit are invalid as anticipated by Stjernschantz, and will thereafter address obviousness.

a. Standard

35. An anticipation inquiry involves two steps. First, the court must construe the

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latanoprost free acid in the body.

claims of the patent in suit as a matter of law. *See Key Phar. v. Hercon Labs. Corp.*, 161 F.3d 709, 714 (Fed. Cir. 1998). Second, the finder of fact must compare the construed claims against the prior art. *See id.* Proving a patent invalid by anticipation "requires that the four corners of a single, prior art document describe every element of the claimed invention, either expressly or inherently, such that a person of ordinary skill in the art could practice the invention without undue experimentation." *Advanced Display Sys. Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000) (citations omitted). The Federal Circuit has stated that "[t]here must be no difference between the claimed invention and the referenced disclosure, as viewed by a person of ordinary skill in the field of the invention." *Scripps Clinic & Research Found. v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991). The elements of the prior art must be arranged or combined in the same manner as in the claim at issue, but the reference need not satisfy an *ipsissimis verbis* test. *In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009) (citations omitted). "In determining whether a patented invention is [explicitly] anticipated, the claims are read in the context of the patent specification in which they arise and in which the invention is described." *Glaverbel Societe Anonyme v. Northlake Mktg. & Supply, Inc.*, 45 F.3d 1550, 1554 (Fed. Cir. 1995). The prosecution history and the prior art may be consulted "[i]f needed to impart clarity or avoid ambiguity" in ascertaining whether the invention is novel or was previously known in the art. *Id.* (internal citations omitted).

36. A prior art reference may anticipate without explicitly disclosing a feature of the claimed invention if that missing characteristic is inherently present in the single

anticipating reference. *See Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991). The Federal Circuit has explained that an inherent limitation is one that is "necessarily present" and not one that may be established by "probabilities or possibilities." *See id.* at 1268-69. That is, "[t]he mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Id.* at 1269 (emphasis in original) (citations omitted).

b. Discussion

37. Defendants argue that Stjernschantz inherently anticipates bimatoprost, as well as methods of treating ocular hypertension or glaucoma using bimatoprost, because bimatoprost is the "natural result flowing from Stjernschantz's explicit disclosure of bimatoprost free acid and its prodrug delivery vehicles." (D.I. 217 at 14-15) (citing *In re Schaumann*, 572 F.2d 312, 316-17 (C.C.P.A. 1978)) A genus of compounds has been held to anticipate a claimed species, but only where the genus contains a very limited number of related compounds. *See In re Schaumann*, 572 F.2d at 316 (concluding that the prior art patent provides a description of a set of 7 chemical compositions resulting in HEP "just as surely as if they were identified in the reference by name," where "claim 1 of the [prior art] patent, read in conjunction with the signification given the expression 'alkyl radical' in the specification, embrace[d] a very limited number of compounds closely related to one another in structure"); *see also In re Petering*, 301 F.2d 676, 681 (C.C.P.A. 1962) (genus of 20 compounds anticipated a non-described subspecies, noting that it was "not the mere number of compounds in this limited class which is significant here but, rather, the total circumstances involved,

including such factors as the limited number of variations for R, only two alternatives for Y and Z, no alternatives for the other ring positions, and a large unchanging parent structural nucleus"); *cf. In re Rusching*, 343 F.2d 965, 974 (C.C.P.A. 1965) (anticipation rejection was inappropriate in view of the lack of a "small recognizable class" of compounds with common properties and cautioning against applying *In re Petering* "to create hindsight anticipations with the guidance of an applicant's disclosures").

38. In support for their anticipation argument, defendants argue that: (1) Stjernschantz teaches that "various modifications of the alpha chain" are possible "while still using the inventive concept" of modifying the omega chain (DTX-822 at 4); (2) amides and esters were acceptable prodrug formulations in the context of ocular drug delivery where the functional group is carboxylic acid; (3) amide and ester prodrugs could be made as a matter of routine; and (4) a person of ordinary skill in the art "would have known that amides were interchangeable with the esters disclosed in Stjernschantz." (D.I. 217 at 16-17) The majority of these arguments are better suited to obviousness than anticipation. Pursuant to defendants' cited caselaw, the question at bar is whether Stjernschantz discloses a small, recognizable class of compounds having a closely-related structure with, and common properties to, bimatoprost, such that a claim to bimatoprost (or method of using it) is anticipated by a disclosure of the Stjernschantz compounds.

39. The court answers in the negative. Stjernschantz states that its inventive feature is the ring structure at the omega chain. (DTX-822 at 22) Stjernschantz discloses that the omega chain can contain many variations (according to the formula C B C – D – R_2, described *supra* at finding 31) and that the ring structure can either be

unsubstituted or have a variety of substituents. (*Id.* at 5) The following description was provided as exemplary of the "various" alpha chains that could be utilized:

> The alpha chain could typically be the naturally occuring alpha chain, which is esterified to the structure
>
> 
>
>
> in which R_1 is an alkyl group, preferably with 1-10 carbon, especially 1-6 atoms, for instance metyl, ethyl, propyl, isopropyl, butyl, isobutyl, neopentyl or benzyl or a derivative giving the final substance equivalent properties as a glaucoma agent. The chain could preferably be a C_6-C_{10} chain which might be saturated or unsaturated having one or more double bonds, and allenes, or a triple bond and the chain might contain one or more substituents such as alkyl groups, alicyclic rings, or aromatic rings with or without hetero atoms.

(DTX-822 at 4-5) Despite the numerosity of potential combinations discussed, Stjernschantz does not disclose any amides at the C1 position. (1010:9-24)

40. As Allergan points out, defendants' inherency argument is not that a Stjernschantz compound metabolizes to bimatoprost, but the reverse – that a disclosure of a prior art metabolite (compound 17) **necessarily** discloses its metabolic precursor because persons of ordinary skill in the art could easily build such precursors.[17] (D.I. 217 at 16-17) The law requires clear and convincing evidence that

[17] *Cf. Schering Corp. v. Geneva Pharmaceuticals, Inc.*, 339 F.3d 1373, 1379-80 (Fed. Cir. 2003) (patent at issue covering a metabolite of loratadine (descarboethoxyloratadine, or "DCL") was anticipated by the disclosure of loratadine, because if a person can infringe a metabolite patent by ingesting a drug and producing the metabolite, "[a]n identical metabolite must then anticipate if earlier in time than the claimed compound") (cited by defendants at D.I. 217 at 18).

bimatoprost is necessarily present **in**, or necessarily created by practicing, Stjernschantz. Defendants point to no expert testimony in this regard, and defendants do not meet their burden here.[18]

3. Obviousness

a. Standards

41. "A patent may not be obtained . . . if the differences between the subject matter sought to be patented 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." 35 U.S.C. § 103(a). Obviousness is a question of law, which depends on several underlying factual inquiries.

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.

KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 406 (2007) (quoting *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)).

42. "[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 550 U.S. at 418. Likewise, a defendant asserting obviousness in view of a

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[18]As discussed *infra*, the court found that defendants' expert lacked credibility. Thus, had anticipation not been precluded on the law, the court would not have found that defendants met their burden to prove invalidity based upon this testimony in any event.

combination of references has the burden to show that a person of ordinary skill in the relevant field had a reason to combine the elements in the manner claimed. *Id*. at 418-19. The Supreme Court has emphasized the need for courts to value "common sense" over "rigid preventative rules" in determining whether a motivation to combine existed. *Id*. at 419-20. "[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." *Id*. at 420. In addition to showing that a person of ordinary skill in the art would have had reason to attempt to make the composition or device, or carry out the claimed process, a defendant must also demonstrate that "such a person would have had a reasonable expectation of success in doing so." *PharmaStem Therapeutics, Inc. v. ViaCell, Inc*., 491 F.3d 1342, 1360 (Fed. Cir. 2007).

43. "Because patents are presumed to be valid, *see* 35 U.S.C. § 282, an alleged infringer seeking to invalidate a patent on obviousness grounds must establish its obviousness by facts supported by clear and convincing evidence." *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 968 (Fed. Cir. 2006) (citation omitted). In conjunction with this burden, the Federal Circuit has explained that,

> [w]hen no prior art other than that which was considered by the PTO examiner is relied on by the attacker, he has the added burden of overcoming the deference that is due to a qualified government agency presumed to have properly done its job, which includes one or more examiners who are assumed to have some expertise in interpreting the references and to be familiar from their work with the level of skill in the art and whose duty it is to issue only valid patents.

PowerOasis, Inc. v. T-Mobile USA, Inc., 522 F.3d 1299, 1304 (Fed. Cir. 2008) (quoting *Am. Hoist &. Derrick Co. v. Sowa & Sons*, 725 F.2d 1350, 1359 (Fed. Cir. 1984)).

b. Expert testimony

44. At trial, defendants offered the testimony of synthetic chemist Dr. Ashim Kumar Mitra ("Mitra") in support of their theory that Stjernschantz renders the claims at issue invalid. Mitra's testimony predominantly focused on obviousness. Mitra opined that bimatoprost is disclosed via Stjernschantz's description of bimatoprost free acid (compound 17), compound 2, and latanoprost (compound 9). (D.I. 211 at 447:12-450:3) Put most simply, bimatoprost is just a "delivery vehicle" for the well known drug (but side-effect prone) bimatoprost free acid. (*Id.* at 447:20) While emphasizing that only Stjernschantz is needed to invalidate the claims (*id.* at 447:12-450:3; 449:14-450:3; D.I. 212 at 523:6-9), Mitra cited additional prior art in support of his opinion. One such reference was unexamined Japanese Patent Application No. S49-69636 ("JP '636") (DTX-994), which Mitra explained would teach an artisan how to convert compound 2 into bimatoprost in one step. (D.I. 212 at 532:10-539:17; 640:24-641:8) While the court does not recant each of the additional references here, it is sufficient to state that none of the additional references were asserted as primary obviousness references.

45. In summing up his testimony, however, Mitra stated that the asserted claims are obvious in view of four references: Stjernschantz, U.S. Patent No. 4,599,353 ("the Bito patent") (DTX-450); JP '636 (DTX-994); and a chapter of a 1977 textbook ("Design of Biopharmaceutical Properties through Prodrugs and Analogs") entitled "Physical Model Approach to the Design of Drugs with Improved Intestinal Absorption" (hereinafter, the "Ho reference") (DTX-998) . (D.I. 212 at 540:17-541:25) Allergan's counsel objected to (and moved to strike) the latter opinion on the basis that it had not previously been disclosed. (*Id.* at 542:20-23) On cross-examination, Mitra reiterated

that Stjernschantz alone invalidates the claims at issue, and stated that he cited additional prior art for the technology for converting compounds 2 and 9 into the amide, bimatoprost. (*Id.* at 564:22-567:5)

46. Mitra's credibility was eviscerated on cross-examination. Allergan's counsel established that Mitra had incorrectly drawn the bimatoprost molecule during his deposition and utilized slides in his trial presentation that incorrectly represented the bond at the C5-C6 position. (*Id.* at 555:2-564:19) Counsel also impeached Mitra with statements made in a 2008 declaration submitted in a prior litigation between Pfizer Canada and Pharmacia Atkiebolag and Pharmascience Inc. (with the Minister of Health) in Canada (hereinafter, the "Canadian litigation").[19] Mitra was retained as an expert in the Canadian litigation by defendants, and opined that Canadian Patent No. 1339132, the Canadian counterpart of Stjernschantz (PTX-1034), was invalid. In the case at bar, Mitra confirmed that he relied on table 6 of Stjernschantz in forming his opinion that the Stjernschantz compounds lowered IOP. (D.I. 212 at 573:17-23) Mitra previously opined, however, that "[t]he [Stjernschantz] experiments in respect of the IOP lowering effects of latanoprost are so flawed that a skilled reader is left in doubts about the usefulness of it." (573:17-584:13) Mitra also previously stated that Stjernschantz's data on IOP lowering "is so deficient that a person skilled in the art

[19]The declaration bears the Canadian federal court docket number T-2221-07. Mitra executed the declaration in May 2008. (PTX-1035)

Defendants objected to the admission of the Mitra's declaration into evidence as hearsay. (D.I. 212 at 578:20-23) Insofar as defendants' counsel had an opportunity to redirect Mitra, the court is inclined to deny the objection. *Federal Rule of Evidence* 613(b). The issue is moot, however, insofar as the court finds Mitra's admissions sufficient without resort to the declaration itself.

would have been in doubt whether latanoprost (and the other tested compounds in this respect) had any effects at all, as all the lowering appears to be within the statistical significance interval." (*Id.*)

47. Mitra explained that, in comparing all of Stjernschantz's IOP data, the data was significant at only one time point, and there was no change between two and four hours. (*Id.*) The clinical trial of latanoprost, however, evidenced a rapid decrease in IOP. Mitra stated that he believes, therefore, that the reported data in Stjernschantz does not show the true effectiveness of latanoprost. (*Id.*) Mitra admitted that the IOP-lowering effectiveness of latanoprost was established subsequent to Stjernschantz through large clinical trials. (*Id.* at 584:9-12) (Stjernschantz "does not disclose data that shows the IOP lowering effects of latanoprost **and** the other tested compounds" in glaucoma patients) (emphasis added)

48. Mitra's credibility was undermined on cross-examination in several additional respects. Mitra admitted that, in 2008, he stated that bimatoprost "is used for the same indications as latanoprost and shows higher IOP-lowering effect." (*Id.* at 598:7-600:13) Mitra first explained that this was in regard to extended-release bimatoprost, but when informed that there is currently no extended-release form of bimatoprost, Mitra said that data he has seen since 2008 has made him believe that bimatoprost and latanoprost are the same. (*Id.*) Mitra confirmed that he previously opined that "bimatoprost acts by a different mechanism than $PGF_{2\alpha}$ derivatives." (*Id.* at 600:14-601:1) Mitra also authored a paper providing that bimatoprost "exerts its action in lowering intraocular pressure (IOP) through a novel prostamide receptor" (PTX-1036

at 488), and that bimatoprost showed "a greater additive response than travoprost. . . which [along with patient response] clearly suggests that these molecules including the free acid forms might stimulate different receptor populations" (*id.* at 489). Mitra claimed that he was only quoting other scientists' work in these regards, and did not necessarily agree with the conclusions. (*Id.* at 602:21-605:19; 606:10-21) As a final example, Mitra stated in a book (slated to publish in February 2011) that, with respect to $PGF_{2\alpha}$ structural analogs, "[b]imatoprost is more efficacious as [an] ocular hypotensive agent than latanoprost and travoprost." (PTX-1033 at 198) Mitra testified that he does not believe that bimatoprost is a structural analog of prostamide $PGF_{2\alpha}$, but that he would not change the pending publication because the conclusion is the work of others. (D.I. 212 at 626:2-628:13)

c. Discussion

49. Defendants' post-trial arguments regarding obviousness differ remarkably from Mitra's testimony at trial. Defendants advance two theories of obviousness post-trial. First, defendants argue that claim 1 of the '649 patent (claiming bimatoprost itself) is obvious in view of JP '636 and "knowledge about the usefulness of the C-17 phenyl substitution." (D.I. 217 at 18) Defendants also argue that all of the asserted claims (to both bimatoprost and the methods for its use) are obvious over Stjernschantz alone or in combination with JP '636, a chapter in the textbook "Prodrugs: Topical and Ocular Drug Delivery" entitled "Improved Ocular Drug Delivery with Prodrugs" (DTX-1006) (hereinafter, "Lee & Bundgaard") bearing a copyright date of 1992, the Bito patent, or the Ho reference.

50. As the court previously indicated, Allergan's counsel objected to Mitra's

opinions that claim 10 of the '819 patent and claims 1-3 of the '619 patent are obvious in view of Stjernschantz, the Bito patent, JP '636, and/or the Ho reference. (D.I. 212 at 540:20-541:25; 542:20-23) Post trial, Allergan argues that defendants waived any obviousness theory that relies primarily on JP '636, or that combines Stjernschantz with Lee & Bundgaard, because defendants failed to introduce any evidence relating to these theories at trial. (D.I. 220 at 26, n.9, 40-41)

51. The court agrees. Defendants in this case clearly present a different theory of obviousness post-trial than was presented at trial. As discussed above, Mitra repeatedly emphasized at trial that Stjernschantz, alone, rendered the claims obvious. Following cross-examination – revealing Mitra's prior sworn statements that Stjernschantz is invalid and publications indicating that bimatoprost outperforms other prostamide $PGF_{2\alpha}$ analogs by interacting with another receptor, as Allergan has maintained – defendants have switched horses by combining pieces of testimony regarding Mitra's secondary references into new obviousness theories. As defendants did not allow Allergan to mount a defense at trial to the JP '636 or Stjernschantz with Lee & Bundgaard theories, the court does not entertain them here.[20] *See, e.g., Broadcom Corp. v. Qualcomm Inc.*, 543 F.3d 683, 694 (Fed. Cir. 2008) (agreeing with district court that claim construction theories first presented post-trial are waived); *Alza Corp. v. Andrx Pharms.*, LLC, 607 F. Supp. 2d 614, 622 (D. Del. 2009) (striking portions of proposed findings of fact post-trial on a written description defense that was not

[20]The court denies as moot Allergan's motion to strike references in defendants' reply brief to an internet web site purportedly showing the publication date of Lee & Bundgaard. (D.I. 229)

presented in pre-trial briefing or during the trial); *Mobil Oil Corp. v. Amoco Chemicals Corp*., 779 F. Supp. 1429, 1441 n.5 (D. Del. 1991) (holding an inventorship defense not presented at trial waived).

52. The court need go no further in finding that defendants have not met their burden to prove, by clear and convincing evidence, that claim 10 of the '819 patent or claims 1-3 of the '649 patent are invalid for obviousness under defendants' remaining theories. As discussed above, the court found Mitra's credibility flawed on a fundamental level. The court simply can assign no weight to Mitra's testimony regarding Stjernschantz's controlling import in view of Mitra's prior opinion and publications. Because they are entirely not credible, the court need not further dissect Mitra's opinions nor render judgment regarding the additional flaws in his reasoning asserted by Allergan.[21] While it found Allergan's expert (and other witnesses) credible, the court also need not detail Allergan's validity evidence, insofar as defendants have not made out a prima facie case of obviousness.[22]

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[21]The court has not located any authority instructing it to review the prior art references and weigh their import absent the guidance of an expert. *Cf. Proveris Scientific Corp. v. Innovasystems, Inc.*, 536 F.3d 1256, 1367-68 (Fed. Cir. 2008) (expert testimony is required to establish invalidity where the subject matter of the patent was sufficiently complex to fall beyond grasp of ordinary layperson); *see also Wyers v. Master Lock Co.,* 616 F.3d 1231, 1240 n.5 (Fed. Cir. 2010) (expert testimony is "critical" in such cases to establish certain features in the prior art "or the existence (or lack thereof) of a motivation to combine references") (citations omitted).

[22]The court denies as moot defendants' motions to strike the opinions and exclude the testimony of Allergan's experts (D.I. 182, 184, 186), the subjects of which primarily concerns secondary indicia of nonobviousness, for example, the "unexpected result" of bimatoprost's binding to a new receptor.

III. CONCLUSION

53. For the reasons discussed above, the court concludes that Allergan has met its burden to prove, by a preponderance of the evidence, that defendants' ANDA product infringes claim 10 of the '819 patent and claims 1-3 of the '649 patent under the court's construction.

54. Defendants have not proven, by clear and convincing evidence, that the '819 and '649 patents are invalid as inherently anticipated by Stjernschantz or as obvious in view of Stjernschantz alone or in combination with other references.