**IN THE UNITED STATES DISTRICT COURT**
**FOR THE DISTRICT OF DELAWARE**

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| ALLERGAN, INC.,<br><br>Plaintiff,<br><br>v.<br><br>BARR LABORATORIES, INC., TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICAL INDUSTRIES, LTD., and SANDOZ INC.,<br><br>Defendants. | Civil Action No. 09-333-SLR-MPT<br><br>**CONSOLIDATED ACTION** |

**DEFENDANTS' JOINT OPENING POST-TRIAL BRIEF**

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## NATURE AND STAGE OF THE PROCEEDINGS

This is a Hatch-Waxman case. Barr and Sandoz filed ANDAs seeking to market generic forms of Allergan's Lumigan® product, containing bimatoprost. This case turns on the invalidity and noninfringement of Claim 10 of U.S. Patent No. 5,688,819 ("the '819 patent") and the invalidity of Claims 1-3 of U.S. Patent No. 6,403,649 ("the '649 patent"). The Court held a five-day bench trial on these issues from January 31 to February 4, 2011. The 30-month stay for Barr—the first filer in the case—expires on or about September 26, 2011.

## SUMMARY OF THE ARGUMENT

The evidence at trial clearly and convincingly established that the asserted claims of the '819 and '649 patents are invalid as anticipated under 35 U.S.C. § 102(b), and as obvious under 35 U.S.C. § 103. In addition, if the Court adopts the claim construction proposed by Defendants, Claim 10 of the '819 patent is invalid under 35 U.S.C. § 112, ¶ 4 for being broader than the claim from which it depends, and would not be infringed by Defendants' ANDA products.

This case is about Allergan's struggle to keep up with its competitors in the market for glaucoma treatments. After failing to develop its own, novel compound, and faced with the launch of a competing product by Pharmacia,[1] Allergan resorted to using a prior art compound well known to be a potent anti-glaucoma drug—bimatoprost free acid—and to administering that drug using a known formulation called a "prodrug."

It had long been known that while bimatoprost free acid lowered intraocular pressure ("IOP"), it was not clinically useful because it was unable to penetrate the cornea easily and caused adverse side effects like hyperemia (redness of the eye) and irritation. To solve that problem, the prior art Stjernschantz reference (DTX-822) disclosed the use of prodrugs of

[1] Pharmacia's product, which contains latanoprost as the active ingredient, is marketed as Xalatan®. Following a merger, Xalatan® is now marketed by Pfizer.

bimatoprost free acid, which are modified versions of the active compound that were known to more easily penetrate the cornea and convert back to the active form in the eye. Allergan's later-claimed bimatoprost is an amide prodrug of bimatoprost free acid.[2] Bimatoprost, as well as methods of using it to treat glaucoma, are thus invalid as anticipated by Stjernschantz.

The asserted claims are also obvious in light of Stjernschantz, alone or when combined with other prior art. Each aspect of Allergan's asserted claims was well known as of 1992: the active ingredient (bimatoprost free acid); a problem to be solved (difficulty penetrating the cornea and resulting side effects); and the formulation that permits delivery into the eye (making a prodrug by substituting an amide group at the C1 position of the bimatoprost free acid compound). There is only one difference between the closest expressly disclosed prior art prodrug and bimatoprost: Pharmacia used ***esters*** at the C1 position to make prodrugs of bimatoprost free acid, while Allergan used an ***amide***. There is nothing inventive about that switch:

- Esters and amides were both known to mask the active, but irritating, bimatoprost free acid so it could be applied topically to the eye.
- Esters and amides were both known to undergo a process called "hydrolysis" in the eye, in which the ester or amide converts back into the active acid form. In fact, the prior art unequivocally suggested that amides would be acceptable prodrug formulations for ocular use that would convert to the active acid form in the eye.
- A person of skill in the art in 1992 was motivated to use amides instead of esters (1) because ester prodrugs of bimatoprost free acid were patented, and (2) in an attempt to decrease remaining adverse side effects of ester prodrugs.

[2] Bimatoprost is a prodrug that substitutes an ethyl amide group at the C1 position of the active acid. *See infra*, Part II.B-F. When bimatoprost is placed in the eye, it converts to bimatoprost free acid. *See, e.g.*, D.I. 210, 101:23-102:3 (Whitcup); D.I. 211, 359:20-23 (Woodward); D.I. 212, 669:13-19 (Chen); *id*. at 689:19-25 (Wheeler); D.I. 213, 921:5-8 (Regan); D.I. 212, 519:23-520:3 (Mitra).

Following this obvious logic, Allergan started making amide prodrugs of $PGF_{2\alpha}$ (a potent prior art IOP-lowering agent closely related to bimatoprost) as part of its glaucoma research program in the late 1980s. DTX-13 at 4-7; PTX-95 at 3-4 (AGN-BAR-00244316-17); D.I. 210:148:3-9 (Garst). Those compounds, while useful for lowering IOP, were put aside because Allergan believed Pharmacia's prior art Bito patent covered all prodrugs of $PGF_{2\alpha}$ with modifications at the C1 position. *See* DTX-450 at col.16 claims 1 and 5; PTX-98 at 27. In an effort to avoid the Bito patent, which Pharmacia controlled, Allergan spent its time modifying other positions on $PGF_{2\alpha}$ and related compounds in the hope of discovering something patentable. That alternative path did not lead to any clinically promising drug candidates.

In 1990, however, Pharmacia disclosed its Stjernschantz patent application covering prodrugs of bimatoprost free acid and related molecules. DTX-822 at 24-26. Allergan learned in 1991 at a conference of the Association for Research in Vision and Ophthalmology ("ARVO") that Pharmacia's compounds—all esters—were undergoing human clinical testing as anti-glaucoma agents. DTX-151. An Allergan employee, June Chen, attended that conference and reported Pharmacia's clinical success with bimatoprost free acid prodrugs to named inventors David Woodward, Michael Garst, and David Burk. PTX-175; DTX-151. Faced with the imminent launch of a competitor's new product, Allergan returned to the prior art amide prodrugs in order to get a product to market, even though (as Allergan admitted) that approach risked a patent infringement lawsuit. Allergan used Pharmacia's compounds as important leads and synthesized bimatoprost—the ethyl amide prodrug of bimatoprost free acid—within months of learning about the clinical successes of Pharmacia's compounds. PTX-391 at 6 (AGN-BAR-02132270); D.I. 212, 673:15-674:22 (Chen); D.I. 210, 178:18-179:22 (Garst). It later launched bimatoprost under the brand name Lumigan®, which is a prodrug that metabolizes to

bimatoprost free acid in the eye. As expected, Pharmacia accused Allergan of infringing the Bito patent (and the U.S. counterpart of the Stjernschantz reference), but the case settled and Lumigan® remains on the market. D.I. 211, 337:4-16 (Woodward); *Allergan Inc., et al. v. Pharmacia Corp., et al.*, No. 01 CV 00141-SLR (D. Del. Mar. 1, 2001).

Because Allergan jettisoned independent research in favor of following the prior art and its biggest competitor, its trial presentation focused on alleged secondary considerations of non-obviousness. Yet it failed to present evidence sufficient to overcome Defendants' strong showing of *prima facie* obviousness. As for "unexpected" results, Allergan labored to argue that bimatoprost does not act as a prodrug of bimatoprost free acid. That argument is an admission that functioning as a prodrug is exactly what a person of ordinary skill would have "expected" bimatoprost to do, consistent with the teachings of the prior art. Moreover, the record shows that every scientist who performed research on the issue—with the sole exception of those associated with Allergan—rejects Allergan's theory that bimatoprost is not a prodrug and acts as an intact amide molecule on a new "prostamide" receptor.

Allergan also failed to establish other secondary evidence. It was unable to show that bimatoprost is a more efficacious drug than Pharmacia's prior art latanoprost (Xalatan®) compound, which to this day outsells Lumigan® by a margin of at least 2 to 1, nor could it relate the alleged superiority to a long-felt need. Allergan also failed to establish that Lumigan® is a commercial success for purposes of an obviousness analysis. Lumigan®'s revenues do not result from anything inventive, but instead reflect a "me too" drug that has not supplanted others in the market. Finally, the only suggestion of "copying" was the irrelevant fact that two generic drug companies filed ANDAs.

Allergan did not present a single witness who is not a current Allergan employee, or who

has not been a long-time Allergan-paid consultant, to try to rebut the invalidity defense. And none of the testimony or opinions its witnesses offered overcame Defendants' strong showing. The totality of the evidence renders the asserted claims invalid as anticipated and obvious.

Additionally, if the Court agrees with Defendants that the claim term "–$N(R^4)_2$" means that the two $R^4$ groups must be identical, then dependent Claim 10 of the '819 patent is invalid under 35 U.S.C. § 112, ¶ 4 and is not infringed by Defendants' ANDA products.

## STATEMENT OF FACTS

### I. The Physiology of Glaucoma

Glaucoma is a disease of the eye in which the optic nerve is damaged and vision loss can result. DTX-450 at col.1 ll.33-35; D.I. 210, 70:2-15 (Whitcup); D.I. 211, 462:3-14 (Mitra). A closely related condition, called "ocular hypertension," occurs when the amount of fluid in the front portion of the eye rises above normal levels. DTX-450 at col.1 ll.24-32; D.I. 210, 70:4-7 (Whitcup); D.I. 211, 460:19-462:5 (Mitra). Ocular hypertension is a risk factor for glaucoma, and many treatments for preventing and managing glaucoma are *hypo*tensive agents, i.e., drugs that reduce IOP. DTX-450 at col.1 ll.22-32; D.I. 210, 70:4-5, 70:17-70:21 (Whitcup); D.I. 211, 462:6-464:15 (Mitra).

### II. Early Work With Prostaglandins

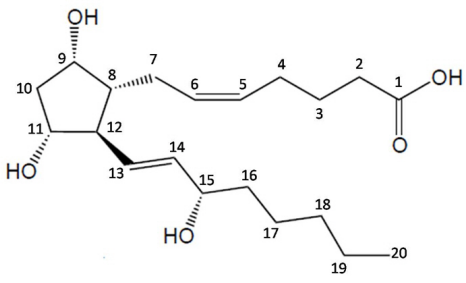



**Fig. 1.** **$PGF_{2\alpha}$**

The potent hypotensive effects of prostaglandin $F_{2\alpha}$ ("$PGF_{2\alpha}$") have been known since at least the early 1970s. DTX-994 at 8; D.I. 211, 468:25-469:5 (Mitra). $PGF_{2\alpha}$ is a naturally occurring prostaglandin molecule with the structure shown in Figure 1. The numbers on this $PGF_{2\alpha}$ structure indicate the twenty carbon atoms that make up its backbone. The chemical group shown at the number "1" position, or "C1," is known as

carboxylic acid, also written chemically as "—COOH." The top part of this hairpin structure is referred to as the alpha chain (C1-C7), and the bottom part is referred to as the omega chain (C13-C20). *See* D.I. 211, 465:15-21 (Mitra).

$PGF_{2\alpha}$ and related compounds cause their physiological effects by activating a biological receptor from a class called "G-protein coupled receptors," or "GPCRs." D.I. 214, 1124:3-1125:6, 1133:6-20 (Sherman). The GPCR these compounds activate is known as the "FP receptor," which Allergan referred to at trial as the "classical FP receptor." *See, e.g.*, D.I. 213, 864:11-17, 871:8-12 (Regan); D.I. 210, 153:1-10 (Garst); D.I. 214, 1133:16-20 (Sherman).

Ophthalmic researchers such as Carl Camras and Laszlo Bito had shown by the late 1970s and early 1980s that one activity of $PGF_{2\alpha}$ was its ability to lower IOP in animals. DTX-995 at 6-7; DTX-991 at 8; DTX-234 at 4; DTX-450 at col.3 ll.14-18; D.I. 211, 468:25-469:9, 477:6-478:22, 479:14-480:10 (Mitra). That conclusion was extended to humans in 1985. DTX-997 at 1; D.I. 211, 481:8-25 (Mitra). Japanese Patent Application No. S49-69636 ("JP '636") also showed in 1974 that altering the acid at the C1 position could result in new molecules that would "demonstrate[] excellent prostaglandin-like (PG) pharmacological activities," including certain "hypotensive" effects. DTX-994 at 8. One compound was $PGF_{2\alpha}$ with an ethyl amide substituent in place of the carboxylic acid at the C1 position. *Id*. at 9; Fig. 2. The prior art thus taught that $PGF_{2\alpha}$ C1 ethylamide had prostaglandin-like activities. *See also* DTX-356 at 34.

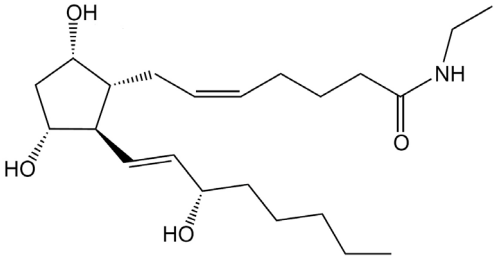



**Fig. 2 $PGF_{2\alpha}$ C1-ethyl amide**

The prior art also taught that one could increase the potency of $PGF_{2\alpha}$ and related compounds by adding a structure called a "phenyl ring" at the C17 position (in the omega chain).

D.I. 214, 1058:25-1059:7 (Macdonald); D.I. 211, 338:23-339:8 (Woodward); *see also* DTX-1008 at 4 ll.34-40, 12 ll.40-61, 13 ll.36-39; DTX-1009 at 4 ll.1-12, 5 l.10, 22 l.20 – 23 l.6; D.I. 213, 1026:10-1027:1 (Macdonald); DTX-1011 at 1, 2. When that modification is applied directly to $PGF_{2\alpha}$, it results in a molecule called "17-phenyl $PGF_{2\alpha}$," also known as "bimatoprost free acid." D.I. 212, 672:11-18 (Chen); D.I. 213, 908:19-22 (Regan); D.I. 214, 1062:4-6 (Macdonald). As shown in Figure 3, it is structurally identical to $PGF_{2\alpha}$, except for the substitution of a C17 phenyl ring.

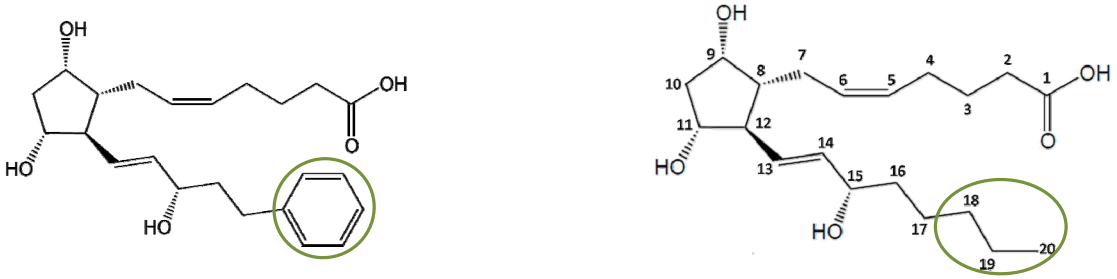



**Fig. 3 17-phenyl $PGF_{2\alpha}$ (bimatoprost free acid)** **$PGF_{2\alpha}$**

Bimatoprost free acid—17-phenyl $PGF_{2\alpha}$—was well known in the prior art as a potent IOP-lowering agent directed to the use of prostaglandins for treating glaucoma. The 1990 Stjernschantz reference disclosed its exact structure precisely for that purpose (DTX-822 at 26, Table II, Compound 17), and there is no dispute that bimatoprost free acid was shown long ago to lower IOP when administered to the eye. D.I. 211, 339:24-340:3 (Woodward); D.I. 210, 220:12-18 (Woodward); D.I. 214, 1064:17-20, 1066:19-23 (Macdonald); D.I. 211, 447:25-448:3 (Mitra). The bimatoprost now claimed by Allergan is identical to bimatoprost free acid with the exception of one simple, known, structural modification designed to increase the ability of active bimatoprost free acid to pass through the outer surface of the eye—substitution of the carboxylic acid at the C1 position with a neutral chemical group, in this case an amide. As discussed further below, the prior art had already applied that type of structural change to bimatoprost free acid. Allergan followed the same, known logic when it synthesized the bimatoprost molecule it now

sells as Lumigan®.

## III. Prostaglandin Prodrug Research

A significant drawback to the direct application of compounds like $PGF_{2\alpha}$ and bimatoprost free acid was that they caused side effects including hyperemia (redness of the eye) and irritation. D.I. 211, 341:1-12 (Woodward); *id*. at 457:22-458:13, 464:23-465:6, 488:11-489:5 (Mitra). The problem stems from the acid at the C1 position. That acid is a charged compound, and charged compounds have difficulty passing through the lipid-rich (i.e., fatty) cornea on the outside of the eye. DTX-13 at 4; D.I. 211, 343:17-344:18, 345:19-346:2 (Woodward); *id*. at 488:19-489:5 (Mitra). The result is not surprising: $PGF_{2\alpha}$ and bimatoprost free acid are acids; when you put acid on the surface of the eye, the result is hyperemia and irritation.

Ophthalmic researchers started to overcome this problem in the mid-1980s using "prodrugs." Prodrugs of $PGF_{2\alpha}$ and its derivatives are modified versions of the active molecules in which the charged C1 carboxylic acid is temporarily replaced with a neutral chemical group that allows the drug to more easily penetrate the lipid-rich cornea. *E.g.*, D.I. 211, 448:20-449:13, 457:1-458:13, 489:16-491:6, 496:19-497:9 (Mitra); *see also* D.I. 210, 136:4-8 (Garst); *id*. at 205:7-12 (Andrews); *id*. at 219:20-220:4 (Woodward); D.I. 211, 344:7-18, 345:19-346:2 (Woodward); D.I. 212, 675:25-676:4 (Wheeler). As they penetrate the eye, those neutral compounds undergo "hydrolysis," a process in which the neutral C1 group reacts with water and enzymes in the eye to re-form the original, active acid compound. *See* DTX-1002 at 3, 5; D.I. 211, 491:7-492:16 (Mitra); D.I. 213, 910:21-911:7 (Regan). Allergan referred to the original bimatoprost free acid compound as the "parent" compound. D.I. 213, 1012:5-8 (Macdonald).

Dr. Bito made and patented lipid soluble $PGF_{2\alpha}$ prodrugs in 1986 for use in lowering IOP. DTX-450 at col.3, ll.20-33, col.16 claims 1, 3, 5, 8; D.I. 211, 497:21-498:22 (Mitra). Only

a few years later, scientists at Pharmacia took the next step of making prodrugs of C17-phenyl substituted molecules, including prodrugs of bimatoprost free acid as disclosed in Stjernschantz. DTX-822 at 25-26. The Stjernschantz disclosure was focused primarily on making prodrugs using a chemical group called "esters" as more neutral replacements of the active C1 acids. *Id*. One particularly relevant disclosure was the ester prodrug of bimatoprost free acid, referred to as Compound 2. DTX-822 at 11, Ex. 2. There is a single structural difference between Compound 2 and the bimatoprost free acid prodrug now claimed by Allergan: Compound 2 has an isopropyl ester at the C1 position, while bimatoprost has an ethyl amide. Fig. 4; D.I. 210, 179:11-14 (Garst); D.I. 214, 1060:1-16 (Macdonald).

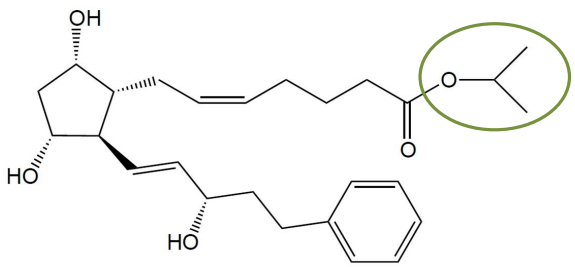
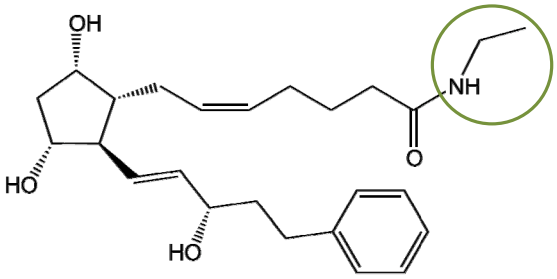



**Fig. 4: Bimatoprost free acid prodrug (isopropyl ester); Compound 2 in Stjernschantz (DTX-822 at 25)**




**Bimatoprost free acid prodrug (ethyl amide); Claimed by Allergan**

When they undergo hydrolysis, both of these compounds convert back to the same active parent compound: bimatoprost free acid, disclosed as Compound 17 in Stjernschantz. DTX-822 at 26; D.I. 211, 491:7-492:16, 524:14-525:20 (Mitra); D.I. 213, 910:21-911:7 (Regan).

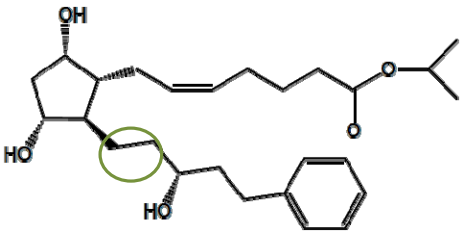



**Fig. 5 Latanoprost**

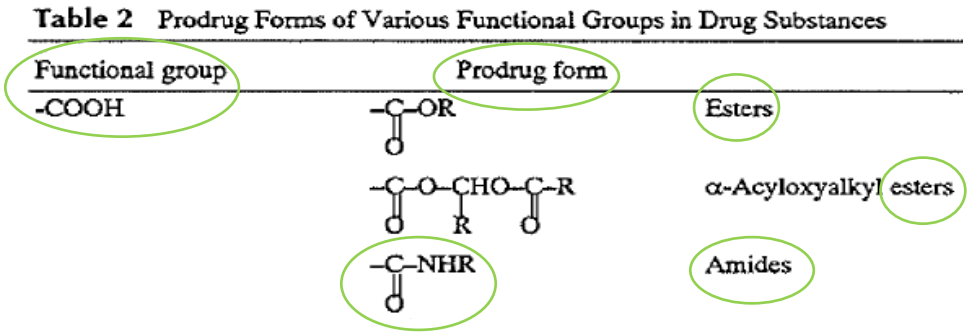
Another related prodrug disclosed in Stjernschantz was Compound 9, which is now chemically referred to as "latanoprost" and marketed as "Xalatan®." D.I. 212, 508:9-20 (Mitra); D.I. 213, 1008:10-15; D.I. 214, 1061:11-13 (Macdonald). Latanoprost is an isopropyl ester prodrug identical to Stjernschantz's Compound 2 (i.e., the bimatoprost free acid prodrug), except latanoprost has only a single carbon bond at the C13-14 position. Fig. 5; D.I. 212, 508:9-20;

528:14-529:3 (Mitra). This makes it less like naturally occurring $PGF_{2\alpha}$, which has a double bond at that location. *See* D.I. 212, 528:15-530:1 (Mitra). Xalatan® is currently the leading prostaglandin anti-glaucoma treatment, beating Lumigan® in prescriptions by a margin of more than 2 to 1. *See* PTX-994 at 5.

Stjernschantz reported the human IOP-lowering effect of only five prodrugs in his patent application, including the bimatoprost free acid prodrug (Compound 2) and latanoprost (Compound 9). Stjernschantz reported that Compound 2 was the most potent, confirming bimatoprost free acid as an effective IOP-lowering agent. DTX-822 at 31; D.I. 212, 507:13-508:8; 508:21-510:2 (Mitra).

The disclosure of Stjernschantz, however, is not limited to ester prodrugs. It expressly teaches that because the "crucial" step was the inclusion of a "ring structure in the *omega chain*," it was still possible to use that same "inventive concept" but make "various modifications of the *alpha chain*" other than the expressly disclosed esters. DTX-822 at 6, 24 (emphases added).

The art as of the claimed 1992 invention date was clear on what those "various modifications" might be. A 1992 textbook called "Prodrugs: Topical and Ocular Drug Delivery," contained a chapter specifically addressing "Improved Ocular Drug Delivery with Prodrugs." DTX-1006 at 3-41. The authors of that chapter, Lee & Bundgaard, stated in unequivocal terms that two of the three available options were esters like those that were the focus of Stjernschantz. The *only* other option listed for making a prodrug that would convert to a carboxylic acid (i.e., "—COOH") functional group in the eye—the conversion that is necessary to make bimatoprost free acid—was amides:




DTX-1006 at 9. Indeed, given that Dr. Bito had a patent expressly covering $PGF_{2\alpha}$ derivatives using esters at the C1 position,[3] the only realistic option for a company seeking to market a new drug was to follow the teachings of Lee & Bundgaard and make obvious amide prodrugs like bimatoprost. *See* DTX-450 at col.16 claim 6; D.I. 212, 665:19-666:1 (Chen); D.I. 211, 313:13-16, 323:1-21 (Woodward); D.I. 212, 680:15-681:5, 688:22-689:10 (Wheeler).

## IV. Allergan's Path To Lumigan® Mirrored Prior Art Teachings.

The essential premise of Allergan's rebuttal case at trial was that the prior art taught unequivocally that amides would not be acceptable prodrugs. *See, e.g.*, D.I. 210, 195:20-196:5 (Andrews); *id*. at 257:12-258:7 (Woodward); D.I. 211, 282:19-22 (Woodward); D.I. 213, 1001:7-10, 1001:24-1002:7 (Macdonald). The facts reveal otherwise.

Not only were amides known in the prior art as acceptable ocular prodrugs, but the art also taught that amide prodrugs were an alternative with the potential to be better than ester prodrugs. What was known in ocular drug textbooks in 1992 was the following: ester prodrugs of $PGF_{2\alpha}$ derivatives like bimatoprost free acid were useful, but their unstable chemical nature could lead to rapid rates of hydrolysis into active, but irritating, acids. *See* DTX-1006 at 8; D.I. 210, 196:17-197:16 (Andrews); D.I. 212, 515:11-516:22 (Mitra). It was also known that ester

[3] As discussed below, Allergan was concerned that Bito claimed all C1 prodrugs, including amides. Bito's claims, for instance, cover treating ocular hypertension or glaucoma with any "$PGF_{2\alpha}$ derivative." DTX-450 at col.16 claim 5. That concern was validated when, shortly after its launch, Pharmacia asserted the Bito patent against Lumigan®. *Allergan v. Pharmacia*, No. 01 CV 00141-SLR.

prodrugs of $PGF_{2\alpha}$ had been expressly patented (DTX-450 at col.16 claims 6, 7, 13-15), that amides were the only other acceptable prodrug formulation for ocular delivery of carboxylic acid (DTX-1006 at 9), and that amides hydrolyzed into acids *more slowly* than esters. D.I. 210, 197:9-16 (Andrews); D.I. 212, 516:7-25 (Mitra); *see also* DTX-1000 at 13. Formulating more stable amide prodrugs was thus an obvious strategy to try, with the predictable result being a compound that converted to free acid and lowered IOP. D.I. 212, 516:7-25 (Mitra); *see also* D.I. 214, 1095:7-1097:7 (Macdonald); *see also, e.g.*, D.I. 211, 359:20-23 (Woodward); *id*. at 689:19-25 (Wheeler); D.I. 213, 921:5-8 (Regan); D.I. 214, 1064:17-20 (Macdonald).

Allergan's suggestion that amides were thought to be unacceptable prodrugs is also belied by the inventors' own research path. Some of the molecules Allergan scientists made were C1 amide forms of $PGF_{2\alpha}$, ("$PGF_{2\alpha}$ C1-CONH2"; "AGN-190911"), which they synthesized for exactly the reason taught by the prior art: amides were "anticipated as *susceptible to metabolism*, thus allowing for *generation of* $PGF_{2\alpha}$"; amides would "be quite effective" in lowering IOP; and amides were hoped to be "much less hyperemic than $PGF_{2\alpha}$." DTX-13 at 4, 7 (emphases added); *see also* D.I. 211, 345:9-346:2, 350:10-17, 350:25-352:8 (Woodward). The first modification they made worked exactly as the prior art suggested. Moreover, as Drs. Woodward and Burk concluded, "we felt that the amidyl moiety [$PGF_{2\alpha}$-C1 amide] was providing us with a compound of the *proper lipophilicity and stability which was lacking with the ester prodrugs of* $PGF_{2\alpha}$." *Id*. at 6-7 (emphasis added). Documents contemporaneously authored by Dr. Garst confirm that Allergan's approach was to synthesize amide prodrugs that would convert back into active $PGF_{2\alpha}$ or its acid derivatives upon application to the eye, and hopefully with fewer side effects than ester prodrugs. PTX-95 at 3 (AGN-BAR-0244316); D.I. 214, 1103:5-22 (Macdonald).

Yet, Allergan put further development of those drugs on hold not because of questions about whether they would work, but because Pharmacia's Bito patent provided "a powerful patent position" covering $PGF_{2\alpha}$ prodrugs. D.I. 212, 680:15-681:5 (Wheeler); *see generally* DTX-450. Allergan viewed that patent as a "Critical Issue" based on the subjective belief that "all $PGF_{2\alpha}$ prodrugs fall within its general scope." PTX-98 at 27 (AGN-BAR-00244542). As a result, Allergan attempted to avoid the compounds claimed in the Bito patent. *Id*.; D.I. 211, 313:13-16 (Woodward); *see also id*. at 317:10-21, 323:1-21. It thus shelved the useful C1-amides and spent years trying to develop other compounds by altering positions other than C1, including C9, 11, and 15, all in an attempt to avoid Bito. D.I. 210, 238:4-19 (Woodward); PTX-98 at 25-27 (AGN-BAR-00244540-542); DTX-13 at 4. Allergan also tried to make compounds that the Bito patent did not cover as part of its "analog" program. D.I. 211, 323:11-21 (Woodward).

Allergan's ultimate decision to return to the amide prodrugs notwithstanding Bito's broad coverage is not surprising given its competitive position in 1992. At an ARVO conference in 1991, Pharmacia publicly released the results of its clinical trials using ester prodrugs of bimatoprost free acid (i.e., Stjernschantz Compound 2) and latanoprost (i.e., Stjernschantz Compound 9). PTX-175; DTX-151; D.I. 210, 165:13-166:6 (Garst); D.I. 211, 324:22-325:11, 326:2-17 (Woodward). Allergan's June Chen attended the conference and made the alleged inventors aware of these developments in May and June of 1991. PTX-175; DTX-151. Without any inventive drug candidates to offer from their own unsuccessful $PGF_{2\alpha}$ "analog" program, Allergan made the decision to return to prodrugs of compounds already known to be effective at lowering IOP in humans, despite the patent infringement risk. *See* D.I. 211, 324:22-325:1 (Woodward); D.I. 212, 673:15-674:22 (Chen). Allergan's Dr. Andrews made bimatoprost within

months after learning of Pharmacia's prodrug successes. PTX-391 at 6 (AGN-BAR 2132270); D.I. 211, 333:24-334:3 (Woodward). Indeed, there was nothing novel about synthesizing bimatoprost; Allergan admitted this was taught in the prior art. D.I 214, 1060:8-1061:2 (Macdonald).

The '819 and '649 patents resulting from Allergan's anticipated and obvious research path include the bimatoprost compound and methods of using it to treat glaucoma or ocular hypertension. Both patents claim priority to an application filed on September 21, 1992. JTX-1; JTX-3. Asserted Claim 1 of the '649 patent is directed solely to the compound bimatoprost. JTX-1 at col.14. Claims 2 and 3 recite methods of treating ocular hypertension or glaucoma by administering a sufficient amount of bimatoprost to the eye. *Id*. Asserted Claim 10 of the '819 patent similarly claims a method of treating ocular hypertension or glaucoma by administering a sufficient amount of any of a number of compounds, one of which is bimatoprost.

## ARGUMENT

### I. The Asserted Claims Are Anticipated.

Stjernschantz inherently anticipates bimatoprost as well as methods of treating ocular hypertension or glaucoma using bimatoprost. Bimatoprost is the natural result flowing from Stjernschantz's explicit disclosure of bimatoprost free acid and its prodrug delivery vehicles. When the Stjernschantz compounds are applied to the eye, they reduce IOP by converting to free acids. This is exactly what happens when bimatoprost is applied to the eye.

#### A. The Law of Inherent Anticipation.

"A patent is invalid for anticipation if a single prior art reference discloses each and every limitation of the claimed invention," either explicitly or inherently. *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003); *In re Omeprazole Patent Litig*., 483 F.3d 1364, 1371 (Fed. Cir. 2007). A single prior art reference may inherently anticipate when it does

not expressly disclose a particular feature of the claimed invention, but the missing feature "is necessarily present, or inherent," in the single prior art reference. *Schering*, 339 F.3d at 1377.

A chemical compound is inherently anticipated if it is the "natural result flowing from the explicit disclosure of the prior art." *Id*. at 1379 (internal quotation omitted). Further, when a prior art reference embraces a very limited number of compounds closely related in structure, the prior art reference provides a description of those compounds "as if they were identified in the reference by name." *In re Schaumann*, 572 F.2d 312, 316-17 (C.C.P.A. 1978). Because bimatoprost is the natural result flowing from the limited number of compounds taught by the Stjernschantz patent, the patents-in-suit are inherently anticipated. Claims covering methods of using bimatoprost to treat ocular hypertension or glaucoma are likewise invalid. *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1376 (Fed. Cir. 2001) (method claims are inherently anticipated when they are "not directed to a new use . . . [but, instead] the same use" as that disclosed in the prior art.); *Abbott Labs. v. Baxter Pharm. Prods., Inc.*, 471 F.3d 1363, 1368-69 (Fed. Cir. 2006).

**B. Stjernschantz Inherently Discloses Bimatoprost And Methods of Its Use.**

Stjernschantz inherently anticipates the asserted method claims. It discloses a method of lowering IOP by administering bimatoprost free acid. DTX-822 at 26, 31. The method claims at issue in this case claim a method of lowering IOP by administering bimatoprost—which automatically converts to bimatoprost free acid in the eye. Defendants established that bimatoprost is simply the delivery vehicle for bimatoprost free acid. D.I. 211, 447:20-24 (Mitra). Specifically, it is an ethyl amide prodrug of bimatoprost free acid, which was known to one of skill in the art and specifically taught in Stjernschantz as Compound 17. *Id*. at 447:25-448:10; D.I. 213, 1008:4-7 (Macdonald). It is undisputed that bimatoprost hydrolyzes to that free acid in the human eye. *See, e.g.*, D.I. 210, 101:23-102:3 (Whitcup); D.I. 211, 359:20-23

(Woodward); D.I. 212, 669:13-19 (Chen); *id*. at 689:19-25 (Wheeler); D.I. 213, 921:5-8 (Regan). This occurs every time a drop of bimatoprost is administered. D.I. 212, 519:23-520:3 (Mitra). The overwhelming evidence at trial shows that bimatoprost free acid is the compound that lowers IOP when Allergan's Lumigan® product is administered. *See infra*, Part II.C.

Stjernschantz also inherently anticipates the bimatoprost compound. It expressly discloses ester prodrug derivatives of bimatoprost free acid useful for treating glaucoma, and inherently teaches the use of amide prodrugs through the teaching that "various modifications of the alpha chain" are possible "while still using the inventive concept" of modifying the omega chain to decrease side effects. DTX-822 at 6. It was general knowledge to persons of skill in the art by 1992 that, in addition to esters, amides were the only other acceptable prodrug formulations in the context of ocular drug delivery where the functional group is a carboxylic acid. DTX-1006 at 9. The use of both amides and esters as prodrugs stems from the basic chemistry knowledge that both groups hydrolyze into acids. *See* D.I. 210, 177:21-178:2 (Garst); D.I. 214, 1070:7-22 (Macdonald). In fact, once that amide is made, its conversion into a carboxylic acid is "automatic" in the presence of water and certain enzymes called amidases present in the eye. D.I. 211, 491:24-493:13 (Mitra); *see also id*. at 493:16-495:11, 495:17-496:22 (Mitra). A person of ordinary skill in the art reading Stjernschantz as of the alleged invention date would thus understand that the "various modifications of the alpha chain" taught by Stjernschantz included only amides, in addition to the expressly disclosed esters, as means for ultimately delivering bimatoprost free acid to glaucoma patients. DTX-822 at 6.

Furthermore, it would have been a routine progression to arrive at the ethyl amide of bimatoprost once amides were chosen. It was known in the art to prepare a series of ester and amide groups when formulating compounds, as one of skill would start with the simplest ester or

amide, and add carbons to create slightly different esters or amides in order to find the group with optimal characteristics for penetration through the eye. *See* D.I. 212, 511:23-515:17 (Mitra); DTX-998 at 50, 59. Dr. Macdonald admitted that a person of skill in the art would have been able to create these simple amides and esters as a matter of routine. D.I. 214, 1060:8-1061:5; s*ee also* D.I. 212, 512:4-513:14 (Mitra). These facts lead to the same invalidity conclusion reached in *In re Schaumann*, 572 F.2d at 312. The claims in *Schaumann* were directed to a single chemical compound and certain of its salts. *Id*. at 313. The claims were rejected in view of a reference that disclosed a general chemical formula with a single variable. *Id*. at 314. In finding the claims anticipated, the court determined that the prior art reference and the disclosed formula embraced only seven compounds that would have been considered. *Id*. at 314, 316-17. Based on that disclosure, the court held that the prior art spelled out a definite and limited class of compounds that enabled a person of skill in the art to at once envisage each of its members, including the later claimed compound. *Id*. at 316-17.

Just as in *Schaumann*, one of skill in the art would have known from Stjernschantz that only a limited number of compounds were useful for making a drug delivery vehicle by masking the active drug metabolite, bimatoprost free acid. Here, persons of skill in the art would have known the group of compounds useful for ocular prodrug delivery comprised only C1 ester or amide substituted compounds, and also would have known that amides were interchangeable with the esters disclosed in Stjernschantz. *See* DTX-998 at 50, 59; D.I. 210, 177:21-178:2 (Garst); D.I. 211, 491:24-493:8 (Mitra); D.I. 212, 511:23-515:17 (Mitra); D.I. 214, 1070:7-22 (Macdonald). Thus, Stjernschantz disclosed a limited class of compounds for use in treating glaucoma that enabled one of skill in the art to deliver bimatoprost free acid into the eye: simple amides and esters, one of which is the now claimed bimatoprost molecule. D.I. 212, 526:10-

527:3 (Mitra).

The facts here are also analogous to those in *Schering*, 339 F.3d at 1373, in which the patent-in-suit was directed to a metabolite of a prior art compound. *Id*. at 1375. Only one structural difference existed between the claimed metabolite and the prior art. *Id.* Moreover, the prior art compound necessarily metabolized to the claimed metabolite once inside the body. *Id*. The prior art thus inherently anticipated the claimed metabolite. *Id.* at 1380 ("An identical metabolite must [ ] anticipate if earlier in time than the claimed compound."). Like in *Schering*, the Stjernschantz prodrugs and the patented prodrug bimatoprost are identical, except for one structural difference: whether the prodrug is a C1 ester or amide. D.I. 214, 1058:8-1060:22 (Macdonald). Either way, the compounds hydrolyze in the eye to form the active bimatoprost free acid. D.I. 212, 525:12-20 (Mitra); D.I. 214, 1092:3-6 (Macdonald).

Bimatoprost is thus the natural result of Stjernschantz's disclosure both of bimatoprost free acid and the usefulness of delivering it as a prodrug for treating glaucoma. Stjernschantz thus inherently anticipates the asserted claims. D.I. 212, 523:4-525:20 (Mitra).

**II. The Asserted Claims Are Invalid As Obvious.**

The prior art references relied on by Defendants at trial support two obviousness theories, both discussed in more detail below. First, the bimatoprost molecule—Claim 1 of the '649 patent—is obvious over at least the JP '636 reference and knowledge about the usefulness of the C17 phenyl substitution. Specifically, JP '636 discloses $PGF_{2\alpha}$ C1-ethyl amide as a compound with potent "prostaglandin-like (PG) pharmacological activities." DTX-994 at 8. It was also known by 1992 (through Stjernschantz and other references, as well as Allergan's admissions) that substituting a phenyl group at the C17 position of $PGF_{2\alpha}$ and related molecules (such as the C1 ethyl amide) is a beneficial change. DTX-822 at 24. Allergan's expert admitted that the 17-phenyl group was a known modification. D.I. 211, 338:23-339:8 (Woodward); D.I. 214,

1058:25-1059:7 (Macdonald). The result of the obvious C17 modification of $PGF_{2\alpha}$ C1-ethyl amide is "17-phenyl $PGF_{2\alpha}$ C1-ethyl amide," otherwise known as bimatoprost.

Second, all of the asserted claims—covering the molecule itself and methods of using it to treat ocular hypertension or glaucoma—are obvious over Stjernschantz, alone or in combination with JP '636, Lee & Bundgaard, the Bito patent, and/or Ho. *See* DTX-822; DTX-994; DTX-1006; DTX-450; DTX-998. Those references lead to the conclusion that it would have been obvious to make, or at least try with a reasonable expectation of success, bimatoprost as a vehicle for delivering bimatoprost free acid to glaucoma patients. Stjernschantz had taught by 1990 that bimatoprost free acid was useful for treating glaucoma and ocular hypertension. *See* DTX-822 at 24, 31. It was also known that bimatoprost free acid could be converted into a prodrug for effective ocular administration with reduced side effects, and that amides were perfectly acceptable ocular prodrug formulations. The art even suggested they might be more effective than prior art ester prodrugs. The combination of these teachings thus did no more than yield a totally predictable result—bimatoprost: a "me too" amide prodrug of bimatoprost free acid useful for treating glaucoma.

### A. Obviousness Is Established When The Asserted Claims Do Nothing More Than Yield Predictable Results.

A claimed invention is obvious and therefore invalid if 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."[4] 35 U.S.C. § 103(a). Applying this standard requires consideration of: (1) the level of ordinary skill in the art; (2) the scope and content of the prior art; (3) the differences between the

[4] A person of ordinary skill in the art would have a Bachelor's, Master's, or Doctorate degree in pharmaceutical chemistry, medicinal chemistry, and/or biochemistry with appropriate experience in industry or academic synthesis, testing, and/or development of ophthalmic drugs and/or prodrugs. D.I. 212, 506:21-507:6 (Mitra). Defendants' analysis and conclusions would not change if the Court adopts Plaintiff's definition of a person of ordinary skill in the art.

claimed invention and the prior art; and (4) secondary considerations of non-obviousness. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007); *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18 (1966); *Purdue Pharma Prods. L.P. v. Par Pharm., Inc.*, 642 F. Supp. 2d 329, 368 (D. Del. 2009).

The Supreme Court emphasized that "the results of ordinary innovation are not the subject of exclusive rights under the patent laws." *KSR*, 550 U.S. at 427. Where an obviousness claim is based on a combination of prior art elements, "the combination must do more than yield a predictable result." *Id*. at 416. In fact, "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *Id.*

Even "the fact that a combination was obvious to *try* might show that it was obvious under § 103." *Id.* at 421 (emphasis added). "In other words, obviousness exists when a 'finite, and in the context of the art, small or easily traversed number of options . . . would convince an ordinarily skilled artisan of obviousness.'" *Purdue*, 642 F. Supp. 2d at 368 (quoting *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008)). That is particularly true where "a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way...." *KSR*, 550 U.S. at 401.

The Federal Circuit has also made abundantly clear that "[o]bviousness does not require absolute predictability of success. . . . All that is required is a reasonable expectation of success." *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (internal quotation omitted); *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). Stated differently, as long as there was a reasonable probability of success, a plaintiff "cannot rebut a defense of obviousness by 'showing some degree of unpredictability in the art . . . .'" *Novartis Pharms.*

*Corp. v. Teva Pharms. USA, Inc.*, No. 05-CV-1887, 2007 WL 2669338, at *8 (D.N.J., Sept. 6, 2007); *see also Pfizer, Inc.*, 480 F.3d at 1364 ("[A] rule of law equating unpredictability to patentability . . . . cannot be the proper standard since the expectation of success need only be reasonable, not absolute.").

The principles set forth in *KSR* are applicable to cases involving chemical compounds. In those instances, "the analysis of the third *Graham* factor (the differences between the claimed invention and the prior art) often turns on the structural similarities and differences between the claimed compound and the prior art compounds." *Eisai Co., Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1356-57 (Fed. Cir. 2008); *see also Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1377 (Fed. Cir. 2006) (for chemical compounds, obviousness is established by demonstrating "structural similarity between claimed and prior art subject matter . . . where the prior art gives reason or motivation to make the claimed compositions."). The flexible nature of the obviousness inquiry set forth in *KSR* still applies. Hence, in compound obviousness cases, the motivation to modify the prior art "can come from any number of sources and need not necessarily be explicit in the art." *Eisai*, 533 F.3d at 1357. "[I]t is sufficient to show that the claimed and prior art compounds possess a sufficiently close relationship . . . to create an expectation, in light of the totality of the prior art, that the new compound will have similar properties to the old." *Id*. (internal quotations omitted).

Under these established standards, the asserted claims were obvious as of 1992.

**B. The Bimatoprost Molecule Was Obvious To Make.**

The first path to a finding of obviousness involves Claim 1 of the '649 patent, which covers the bimatoprost compound. JTX-1 at col.14. That claim is obvious over the JP '636 reference in view of the level of ordinary skill in the art by 1992. DTX-994.

The JP '636 reference disclosed a compound referred to as $PGF_{2\alpha}$-ethyl amide. DTX-994

at 9 (Example 2). It further taught that this compound "demonstrates excellent prostaglandin-like (PG) pharmacological activities." DTX-994 at 8. The only difference between bimatoprost and $PGF_{2\alpha}$-ethyl amide is that the latter does not have a phenyl ring substituted at the C17 position. D.I. 211, 474:25-475:12 (Mitra); Fig. 6.

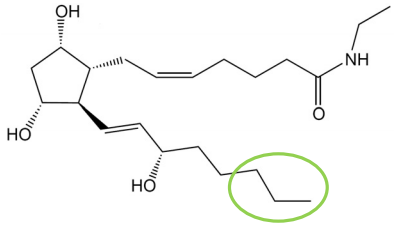
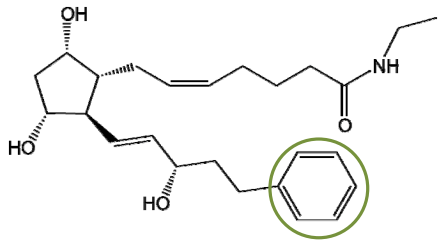



**Fig. 6: $PGF_{2\alpha}$-ethyl amide compound. DTX-994 at 9.**




**Bimatoprost compound. Claimed by Allergan.**

But there is no reasonable dispute that making that C17 phenyl group substitution was entirely obvious. Even before Stjernschantz, the C17 phenyl group had been known as a technique for increasing the potency of $PGF_{2\alpha}$ and related compounds. Great Britain Patent Specification No. 1324737 ("GB '737") and Canadian Patent No. 986926 ("CA '926") disclosed the potent effects of that substitution as early as the 1970s. DTX-1008 at 4 ll.34-40; *id*. at 12 ll.46-61; *id*. at 6, formulas XV-XVII; DTX-1009 at 4 ll.11-12; D.I. 213, 1026:10-1027:1 (Macdonald); D.I. 212, 534:10-25; 535:23-536:9 (Mitra); *see also* DTX-1010 at 5, Fig. 1(a); DTX-1011 at 1, 2; D.I. 212, 536:20-539:17 (Mitra). Stjernschantz then taught in 1990, and directly in the context of glaucoma treatments, that the C17 phenyl ring substitution resulted in significantly reduced IOP, with fewer side effects than $PGF_{2\alpha}$ and related compounds. DTX-822 at 21-24. Bimatoprost is nothing more than an obvious attempt to obtain the benefits of the C17 phenyl substitution for the prior art $PGF_{2\alpha}$-ethyl amide.

Every one of Allergan's witnesses who addressed the issue admitted that substituting the phenyl group at C17 was an obvious modification as of 1992. D.I. 213, 1026:10-1027:1 (Macdonald) (stating that the prior art taught "the substitution of 17-phenyl at that site to

improve binding or activity and metabolism or stability."); D.I. 211, 338:23-339:8 (Woodward) ("[T]he 17-phenyl ring has been known since . . . the mid-1970s. It's not anything new. . . . It has been known for a very, very long time."); *id*. at 311:22-312:4 (Woodward); *see also* D.I. 214, 1058:25-1059:7 (Macdonald) (agreeing that the 17-phenyl substitution was "very well-known in the art."). Dr. Macdonald also confirmed that a person of ordinary skill in the art had the knowledge to make that change and synthesize the entire bimatoprost molecule by 1992. D.I. 214, 1060:8-1061:2; *see also KSR*, 550 U.S. at 417 ("If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability.").

Claim 1 of the '649 patent—i.e., bimatoprost—is thus invalid as obvious with nothing more than the knowledge that the potent $PGF_{2\alpha}$ C1-ethyl amide compound known from JP '636 could be made even more potent by substituting a C17 phenyl ring. The increased potency and decreased side effect profile potentially available from that substitution is more than sufficient motivation for a person of ordinary skill in the art to modify the prior art to arrive at bimatoprost.

**C. Making Bimatoprost And Using It For Treating Glaucoma Was Obvious.**

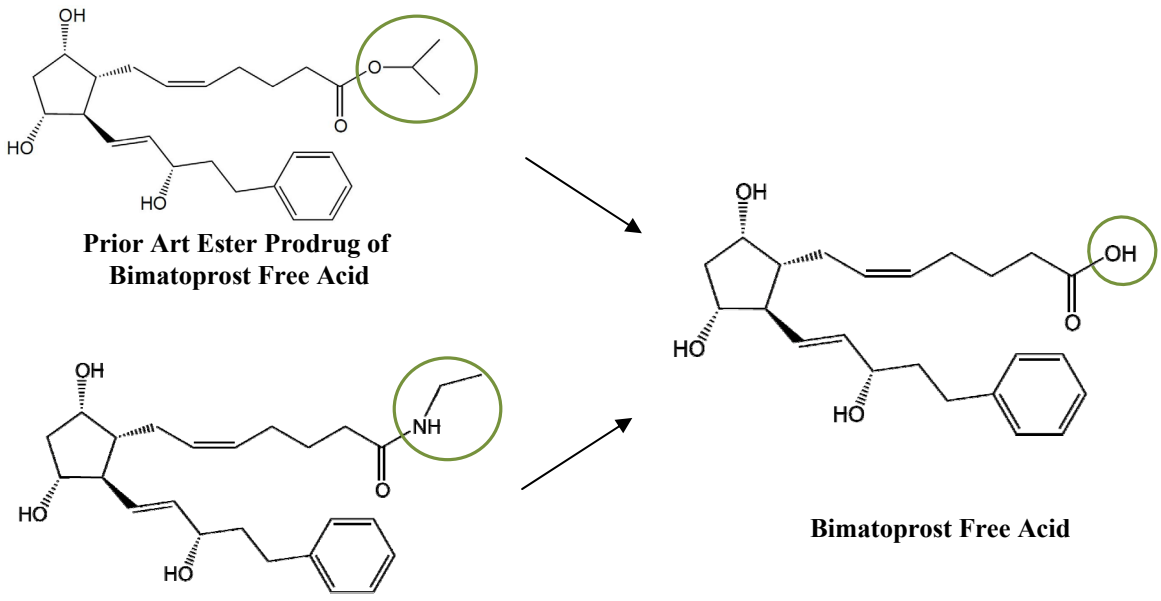
The second path to an obviousness finding involves all of the asserted claims, including bimatoprost and methods of using it to treat glaucoma and ocular hypertension. In particular, the asserted claims are obvious over Stjernschantz, alone or in combination with the teachings of Lee & Bundgaard, JP '636, the Bito patent, and/or Ho. *See* DTX-822; DTX-1006; DTX-994; DTX-450; DTX-998.

The analysis begins with the understanding that Stjernschantz expressly disclosed two anti-glaucoma agents that Allergan's expert, Dr. Macdonald, agrees have only a single structural change from bimatoprost. DTX-822 at 25-26; D.I. 214, 1060:1-7 (Macdonald). The first is Compound 2, shown above (Fig. 4), which has an ester at the C1 position instead of the ethyl amide in bimatoprost. DTX-822 at 25-26; *see also* D.I. 210, 176:12-16 (Garst); D.I. 214,

1058:22-1060:4 (Macdonald). Next is Compound 17, also known as bimatoprost free acid (Fig. 3), (D.I. 214, 1063:2-1064:7 (Macdonald)), which has a carboxylic acid at the C1 position instead of an ethyl amide. *Id*. at 1059:23-25; DTX-822 at 26. The only difference is in the components at the C1 position. D.I. 214, 1060:1-7 (Macdonald).[5]

The obviousness dispute under this reasoning thus boils down to one question: Was it predictable in 1992 that delivering bimatoprost free acid as an amide prodrug would treat glaucoma, when it was known that bimatoprost free acid lowered IOP and that amide prodrugs would hydrolyze into bimatoprost free acid in the eye? To put it graphically, Defendants contend that where the prior art expressly disclosed prodrugs of bimatoprost free acid for the treatment of glaucoma, making an amide prodrug of bimatoprost free acid for that purpose does nothing more than yield a predictable result:

**Fig. 7**




**Prior Art Ester Prodrug of Bimatoprost Free Acid**

**Amide Prodrug of Bimatoprost Free Acid, Claimed by Allergan**

**Bimatoprost Free Acid**

[5] Stjernschantz also discloses Compound 9, latanoprost, which has an additional structural change: a single carbon bond at the C13-14 position, rather then the double bond in bimatoprost. DTX-822 at 25. The double bond in bimatoprost is a more obvious choice, as it is the type of bond that exists in naturally occurring $PGF_{2\alpha}$. D.I. 212, 528:15-530:1 (Mitra).

Defendants proved by clear and convincing evidence that the change to an amide was an obvious modification of the Stjernschantz compounds in view of the level of ordinary skill in the art in 1992. The Bito patent confirmed the usefulness of ocular prodrugs and provided the motivation—patent claims—for a person of ordinary skill to choose prodrug forms other than esters. DTX-450. It was textbook knowledge by 1992 that amides were the only other acceptable ocular prodrugs for carboxylic acid functional groups. DTX-1006 at 9. The prior art JP '636 and Ho references had also long before confirmed the effectiveness of amide modifications to $PGF_{2\alpha}$ molecules. DTX-994 at 8-9; DTX-998 at 50. That knowledge, and Allergan's own internal documents discussed further below, show that a person of ordinary skill in the art, faced with a "finite number of identified, predictable solutions," would have "anticipated success" in synthesizing and using bimatoprost for the treatment of glaucoma. *See KSR*, 550 U.S. at 421.

The parties and their experts are in full agreement as to the fundamental points leading to that conclusion.

**1. Bimatoprost Free Acid Was Known To Lower IOP.**

First, there is no dispute that bimatoprost free acid had "been known for a very long time" prior to the 1992 priority date of the patents in suit. D.I. 211, 339:24-340:3 (Woodward); D.I. 210, 220:12-18 (Woodward); *see also* D.I. 214, 1062:4-6, 1064:17-20, 1066:19-23 (Macdonald); D.I. 211, 447:25-448:10 (Mitra). Bimatoprost free acid was expressly disclosed and diagrammed in Stjernschantz as Compound 17. DTX-822 at 26; D.I. 212, 521:15-522:3 (Mitra). Not only was it known prior to 1992, but it was commercially available from chemical supply companies. DTX-822 at 11, Ex. 2.

Dr. Macdonald—an Allergan expert who has been working with the company since at least 1989 (D.I. 214, 1052:15-1053:6, 1053:21-1054:1)—also readily acknowledged that

"everybody knew bimatoprost free acid back in 1992 would lower IOP" when administered to humans. D.I. 214, 1066:19-23; *see also id.* at 1064:17-20; D.I. 211, 447:10-448:7 (Mitra); D.I. 213, 510:9-18 (Mitra).

**2. Administering Bimatoprost Free Acid Directly To The Eye Was Undesirable.**

Second, despite the known efficacy of bimatoprost free acid before 1992, it was also known that it was undesirable to administer that compound directly to the eye. D.I. 214, 1064:21-1065:11, 1066:24-1067:2 (Macdonald). Bimatoprost free acid was too irritating to be of any practical clinical use. *See id*. at 1064:21-1065:6 (Macdonald). The irritating effect of potent acids in human eyes had been known since at least 1985, when the first use of $PGF_{2\alpha}$ in human eyes caused "side effects of ocular pain, conjunctival hyperemia and headache, which could discourage their use in chronic therapy." DTX-997 at 3; D.I. 211, 341:1-12 (Woodward).

**3. Prodrugs of Bimatoprost Free Acid And Other Prostaglandin Derivatives Solved The Problem Of Direct Administration Of Acids.**

Third, because of the undesirability of administering active acids directly to the eye, scientists in the prior art turned them into prodrugs to increase their clinical effectiveness.

The concept of designing ocular prodrugs specifically for delivery of $PGF_{2\alpha}$ and related compounds was known since at least the issuance of the Bito patent in 1986. DTX-450. The first step in understanding how ocular prodrugs work is understanding that the C1 carboxylic acid of those drugs poorly penetrates the cornea on the surface of the eye. *Id*. at col.14 ll.39-40; D.I. 210, 137:12-19 (Garst); *see also id*. at 205:7-12 (Andrews). That poor penetration is due to the fact that the carboxylic acid is an ion with an electrical charge. Those charged ions are generally repelled by fatty tissues, such as those that make up the cornea. D.I. 211, 460:7-9, 488:25-489:5 (Mitra). Poor penetration then results in remaining acid on the surface of the eye, which was thought to be the reason $PGF_{2\alpha}$ and related compounds caused irritation and

hyperemia. *Id*. at 486:16-487:7, 488:12-22 (Mitra).

The prior art's solution to that problem was the creation of prodrugs, which involves temporarily substituting the active acid with a more neutral chemical group that can more readily penetrate the cornea. D.I. 210, 220:12-18 (Woodward); D.I. 214, 1067:3-15 (Macdonald); DTX-450 at col.14 ll.36-59. Such C1-substituted compounds would not lose their IOP-lowering potency because they were designed to convert *back* into the parent drug after being applied to the eye. D.I. 214, 1067:8-15 (Macdonald); D.I. 212, 507:20-508:8 (Mitra). That conversion, called hydrolysis, occurs when the neutral group—for instance, an amide as in the case of bimatoprost—reacts with water and enzymes in the eye. The result is a change from the neutral group to the active acid. D.I. 211, 491:1-23 (Mitra). Prodrugs are therefore viewed as drug delivery vehicles useful in introducing active C1 acid parent compounds into the eye. D.I. 211, 447:16-24, 448:23-449:1 (Mitra).

Both Bito and Stjernschantz expressly disclose making prodrugs of $PGF_{2\alpha}$ and various $PGF_{2\alpha}$ derivative compounds, including latanoprost and prodrug forms of bimatoprost free acid. DTX-450 at col.16 claims 1 and 5; DTX-822 at 6, 8, 24-26. Compound 2 of Stjernschantz is an isopropyl ester prodrug form of bimatoprost free acid. DTX-822 at 8, 25-26; D.I. 212, 508:3-8 (Mitra). Once administered as a drop in the eye, the ester is hydrolyzed to the carboxylic acid, thereby giving back the bimatoprost free acid parent drug and ultimately lowering IOP. D.I. 212, 508:3-8 (Mitra); *see also* D.I. 214, 1064:9-14 (Macdonald). Stjernschantz even tested that compound for its IOP-lowering effect in humans and showed that it was the most efficacious of all of the compounds tested. DTX-822 at 31; D.I. 212, 508:21-510:20 (Mitra); *see also id*. at 525:21-526:9. Stjernschantz also disclosed latanoprost, which is a prodrug of a $PGF_{2\alpha}$ modified compound that has only a single carbon bond at the C13-14 position (Fig. 5). DTX-822 at 8, 25

(Compound 9). It was shown by Stjernschantz to have IOP-lowering capacity, and has gone on to become the best-selling prostaglandin for glaucoma patients—Xalatan®. DTX-822 at 31; PTX-994.

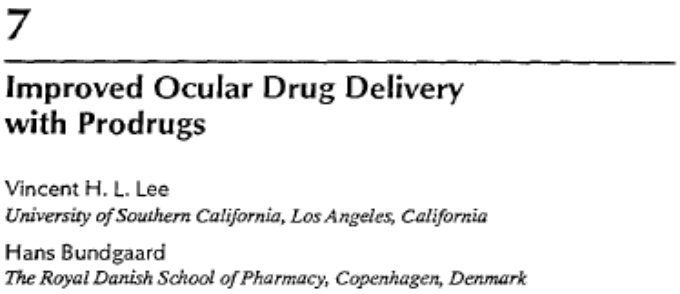
Allergan does not dispute that masking the C1 carboxylic acid with a neutral moiety is disclosed in the prior art. D.I. 214, 1065:19-1066:10, 1067:7-1068:8 (Macdonald); *see also* D.I. 211, 387:10-16 (Woodward); D.I. 210, 137:10-19 (Garst).

**4. Amide Prodrugs Such As Bimatoprost Were Available Choices For Prodrug Formulations.**

**a. Amides Were Known To Be Useful As Prodrugs.**

Fourth, a person of ordinary skill in the art as of 1992 would have fully expected that amide prodrugs of $PGF_{2\alpha}$ derivatives—for example, bimatoprost—would convert into the active free acid moiety when applied to the eye, just like the esters expressly disclosed in Stjernschantz.

Allergan admitted that masking the C1 carboxylic acid of $PGF_{2\alpha}$ with an amide moiety was a generally known technique as of 1992. D.I. 212, 676:8-677:10 (Wheeler); D.I. 214, 1072:9-1073:8 (Macdonald). In fact, amide prodrugs were *expressly* disclosed in the literature—including *textbooks*—as acceptable options for ocular drug delivery as of 1992. DTX-1006 at 9; D.I. 214, 1078:23-1079:10, 1083:21-1084:2 (Macdonald). The clearest evidence of this is the 1992 Sloan text, titled "Prodrugs: Topical and Ocular Drug Delivery," which contains an entire chapter dedicated to exactly this issue:



7

Improved Ocular Drug Delivery with Prodrugs

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DTX-1006 at 3. Lee & Bundgaard show in the most unequivocal terms, that amides as a class

are acceptable prodrug formulations of compounds whose functional group (like bimatoprost) is carboxylic acid ("—COOH"), and reflects the knowledge that an amide will hydrolyze to the carboxylic acid inside the eye:

**Table 2** Prodrug Forms of Various Functional Groups in Drug Substances

| Functional group | Prodrug form | |
|---|---|---|
| -COOH | –C(=O)–OR | Esters |
| | –C(=O)–O–CHR–C(=O)–R | α-Acyloxyalkyl esters |
| | –C(=O)–NHR | Amides |

*Id*. at 9. Lee & Bundgaard thus taught in 1992, in a reference directed to ophthalmic researchers designing drugs for delivery to the eye, that amides were a perfectly acceptable prodrug form for bimatoprost free acid.

Allergan cannot avoid the relevance of this reference. D.I. 214, 1082:15-1083:20 (Macdonald). Dr. Macdonald admitted that an amide prodrug form of a functional carboxylic acid, like bimatoprost, would convert to that acid. *Id*. at 1084:16-1085:1.[6] Indeed, he admitted that Lee & Bundgaard suggest that an amide could be used as a prodrug. *Id*. at 1079:6-10. Allergan's Dr. Wheeler also acknowledged that Lee & Bundgaard had "proposed" the precise modification Allergan made in this case—replacing the carboxylic acid with an amide in order to make a prodrug. D.I. 212, 676:8-15. Dr. Wheeler recognized that the prior art taught that the carboxylic acid could be replaced with amides. *Id*. at 676:16-20 (emphasis added). He further admitted that, based on Lee & Bundgaard, "[o]ne could conceive of using [an amide] as a prodrug." *Id*. at 677:3-10.

[6] Defendants object to the testimony of Dr. Macdonald concerning obviousness for the reasons set forth in their *Daubert* motion. *See* D.I. 182, 183, 201.

**b. $PGF_{2\alpha}$ C1 Amides Were Known to Result in Prostaglandin-Like Activities.**

It was then a simple task to arrive at the particular amide—ethyl amide—used in bimatoprost. Several other prior art references specifically disclosed the ethyl amide as a possible C1 modification of $PGF_{2\alpha}$ compounds. The JP '636 publication taught as early as 1974 the synthesis of $PGF_{2\alpha}$ with an ethyl amide substitution in the C1 position, DTX-994 at 9; D.I. 211, 470:22-471:6, 474:19-475:12, 476:17-477:1 (Mitra), and Dr. Macdonald did not dispute that a person of ordinary skill would have known how to synthesize bimatoprost in 1992. D.I. 214, 1060:8-1061:2; *see also KSR*, 550 U.S. at 417 ("If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability.").

Beyond mere synthesis, the JP '636 also taught that $PGF_{2\alpha}$ C1-ethyl amide "demonstrated excellent prostaglandin-like (PG) pharmacological activities." DTX-994 at 8, 9; *see also* DTX-356 at 34 (publishing in 1990 that $PGF_{2\alpha}$ C1 amides are active in the cat iris sphincter assay). Among the most relevant of those "pharmacological activities" was its "hypotensive" effect, which is precisely the mechanism of action by which bimatoprost lowers IOP. *Id.*; D.I. 211, 470:3-472:3 (Mitra); *see also* D.I. 214, 1066:19-23 (Macdonald). Dr. Macdonald's unfounded testimony that the JP '636 reference is just "a method for manufacturing or synthesizing the prostaglandin amides" is plainly incorrect. D.I. 213, 1016:6-11, 17-23 (Macdonald). Allergan's unsupported suggestion that bimatoprost's activity is surprising is completely contradicted by this prior art, which shows that $PGF_{2\alpha}$ C1-ethyl amide is a potent compound. DTX-994 at 8, 9; D.I. 211, 470:20-472:3 (Mitra).

$PGF_{2\alpha}$-ethyl amides were also disclosed in the literature as prodrugs designed to increase permeability of the parent drugs through biological tissue, just as their use in the ocular context was intended to increase permeability through the cornea. In another prior art textbook titled

"Design of Biopharmaceutical Properties through Prodrugs and Analogs," DTX-998 at 1, a chapter by Ho et al. teaches how to optimize permeability of $PGF_{2\alpha}$ derivatives through the substitution of the carboxylic acid with a small set of amides, including the ethyl amide. *Id.* at 5, 50 (Table VIII); D.I. 212, 511:19-513:14 (Mitra); D.I. 213, 1019:1-8 (Macdonald) (confirming that Ho does "describe or address the permeability coefficient of various prostaglandins or their derivatives, and they describe amide[s] and esters in this particular case."). Ho teaches that if one has a high-activity compound such as $PGF_{2\alpha}$, one can optimize its pharmaceutical and biological properties (including altering absorption rates and decreasing side effects) by "modification of the lead compound via derivative or analog synthesis." DTX-998 at 5. The ethyl amide "modification" made to the $PGF_{2\alpha}$ lead compound in this reference is nearly identical to the structure of bimatoprost, with the exception of the obvious phenyl ring at the C17 position. *Id*. at 48, 50 (Table VIII ($PGF_{2\alpha}$ $C_1$-ethylamide)).

Dr. Macdonald misstated that Ho teaches that esters are preferred over amides in the intestine, thereby suggesting that Ho teaches away from the use of amides. D.I. 213, 1019:9-16. That is incorrect. Ho did not even test the permeability of a series of ester groups, and made no statement that esters were in any way more desirable than amides. But Ho did report *actual* test results about the effective permeability of six amide groups, one of which was the ethyl amide. DTX-998 at 50 (Table VIII). Therefore, Ho does not teach away from the use of amides, but it does teach to test this short series of amide groups, including ethyl amides, to determine which will have optimal permeability through a particular membrane. D.I. 212, 511:23-512:25 (Mitra).

Allergan gains no traction by arguing that the JP '636 and Ho references did not address the specific use of $PGF_{2\alpha}$-ethyl amide for ocular use. First, that argument ignores that Lee & Bundgaard *did* teach that amides are acceptable prodrug formulations *for ocular use*. DTX-1006

at 3, 9. Second, as Allergan's Dr. Wheeler admitted, a person of skill in the art in 1992 knew full well that ocular tissues contain amidase enzymes that will cause hydrolysis of C1 amide groups. D.I. 212, 689:19-25; D.I. 211, 494:5-495:11, 496:7-18 (Mitra). Defendants presented several additional prior art references showing exactly that, and it was not an inventive leap to make the transition from non-ocular activity to applications in the eye. DTX-1000; DTX-1001 at 3-4; DTX-1002 at 3 (disclosing prior to 1992 that amides hydrolyze in ocular tissues). Dr. Macdonald does not dispute this point, having admitted that amides "will hydrolyze into carboxylic acid in the human body," and that there is "no art that says they won't do that in the eye." D.I. 214, 1089:11-16; *see also id*. at 1077:19-1078:1. His argument is also irrelevant, because an obviousness analysis "need not seek out precise teachings directed to the specific subject matter of the challenged claim . . . ." *KSR*, 550 U.S. at 418. Rather, "a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.*

**5. Amide Prodrugs Such As Bimatoprost Were An Obvious Modification To Ester Prodrugs In Ocular Drug Delivery.**

Finally, the record makes clear that developing an amide prodrug as identified by Lee & Bundgaard was an obvious choice for ophthalmic pharmaceutical researchers like those at Allergan. In fact, amides were effectively the *only* available option because ester prodrugs had been patented. Bito's express coverage of ester prodrugs of "$PGF_{2\alpha}$ derivatives" provided good reason for Allergan and other pharmaceutical companies to avoid ester prodrugs, lest they develop a product that infringed Pharmacia's intellectual property. DTX-450 at col.16 claims 1-19; *see also infra*, Part II.D.

A person of ordinary skill would also have been motivated to try developing amide prodrugs of bimatoprost free acid in an effort to try optimizing the existing ester prodrugs. The

ester prodrugs patented by Bito and Stjernschantz, while clinically useful, did not entirely eliminate side effects like hyperemia. D.I. 214, 1091:24-1092:11 (Macdonald); D.I. 212, 527:4-12 (Mitra); *see also, e.g.*, DTX-822 at 28. Those remaining side effects were thought to be caused by the fact that ester prodrugs were susceptible to rapid hydrolysis. D.I. 214, 1092:12-22, 1097:10-1098:3 (Macdonald). That is, the esters would quickly hydrolyze into the functional carboxylic acid group. *See* D.I. 212, 668:21-669:4 (Chen); *id*. at 676:21-677:2 (Wheeler); D.I. 211, 491:17-492:21 (Mitra); DTX-12 at 35. The hydrolysis of esters near the surface of the eye occurred quickly, which may have led in some cases to higher concentrations of the irritating free acid and, thus, hyperemia. *See* D.I. 214, 1092:12-22, 1097:10-15 (Macdonald). The possibility of rapid hydrolysis was specifically referenced by Lee & Bundgaard, who taught that "[e]ven when esterification is feasible, ester prodrugs may create problems owing to chemical instability in aqueous eye drops formulations." DTX-1006 at 8; *see also* D.I. 214, 1085:16-1086:24 (Macdonald). They continued, noting that "[s]uch cases will be discussed below along with . . . some newly developed *nonester* prodrug types that have been or may be applied to ophthalmic drugs." DTX-1006 at 8 (emphasis added).

The other "nonester prodrug type" they taught as a possible means to address the "chemical instability" of esters was amides. DTX-1006 at 8-9; D.I. 214, 1086:11-1087:1 (Macdonald). That is because amides are more stable and hydrolyze more slowly than esters. D.I. 214, 1097:25-1098:3, 1089:5-1089:9 (Macdonald); D.I. 212, 690:1-4 (Wheeler); D.I. 212, 516:7-11 (Mitra); DTX-1000 at 1, 13. Accordingly, a person of ordinary skill in the art would have had the motivation to try ocular amide prodrugs of bimatoprost free acid, as taught by the prior art, in an effort to further decrease the incidence of ocular side effects. D.I. 212, 516:7-25 (Mitra); *see also* D.I. 214, 1095:7-1096:4, 1096:15-1097:8 (Macdonald).

One of ordinary skill in the art in 1992 thus would have been motivated to try making and using a prodrug that: (1) had not been expressly patented; and (2) incorporated a chemical group with a slower rate of hydrolysis than esters, such as amides. *See, e.g.*, D.I. 210, 189:24-190:15 (Andrews); D.I. 212, 515:11-516:25, 526:2-527:12, 529:24-530:5 (Mitra); D.I. 214, 1095:1-6 (Macdonald).

**D. Allergan's Actions Confirm That Bimatoprost Was An Obvious Choice.**

Allergan and its experts suggested at trial that one never would have tried a C1 amide substitution with any expectation of success. That story is directly contrary to what the art actually taught, as discussed above, as well as Allergan's own actions.

Allergan's contemporaneous documents, created long before this litigation, confirm that its scientists never thought amides would be non-efficacious "antagonists" that would not work as prodrugs. To the contrary, Allergan's scientists synthesized amide *prodrugs* of $PGF_{2\alpha}$ as early as 1987, which Dr. Macdonald admitted were made with the understanding that $PGF_{2\alpha}$—with a C1 carboxylic acid—would result. D.I. 214, 1102:7-11 (Macdonald); PTX-393; PTX-88; PTX-89; *see also* DTX-13 at 4 (disclosing synthesis of an amide, with the chemical notation "$PGF_{2\alpha}$ C1-CONH2"); D.I. 212, 682:4-23 (Wheeler). Those amide prodrugs were expressly disclosed in the prior art, and Dr. Woodward admitted that there is not a "big difference" between the chemical structure of those molecules and bimatoprost. D.I. 211, 357:11-21; PTX-452 at 2 (Fig. 1) (AGN-BAR-02154122).

Just as the art suggested, Dr. Woodward tried modifying the known ester prodrugs by making amides. His belief was that those amides would be acceptable prodrug options because they "were anticipated as susceptible to metabolism, thus allowing for generation of $PGF_{2\alpha}$." DTX-13 at 4. That is, like a person of ordinary skill in the art in 1992, Dr. Woodward fully expected the $PGF_{2\alpha}$-C1 amide to hydrolyze to $PGF_{2\alpha}$ once applied to the eye. And just as a

person of ordinary skill in the art would have expected, he found the amide compound to "be quite effective" in lowering IOP and "much less hyperemic than $PGF_{2\alpha}$." *Id*. at 4, 7. As Drs. Woodward and Burk stated, "we felt that the amidyl moiety [i.e., $PGF_{2\alpha}$-C1 amide] was providing us with a compound of the *proper lipophilicity and stability which was lacking with the ester prodrugs of* $PGF_{2\alpha}$." *Id*. at 6-7 (emphasis added).

But Allergan shelved those amides because of its own subjective belief that Pharmacia's Bito patent provided "a powerful patent position" covering all $PGF_{2\alpha}$ prgodrugs. D.I. 212, 680:15-681:5 (Wheeler); DTX-450. Allergan had even identified the Bito patent as a "Critical Issue" in connection with its prodrug development program, and expressed concern that "all $PGF_{2\alpha}$ prodrugs fall within its general scope." PTX-98 at 27 (AGN-BAR-00244542). Dr. Woodward's concern about Bito was so serious that he wrote multiple memos to Allergan's legal department setting out his thoughts supporting an invalidity argument. *Id*.; DTX-181 at 1; DTX-183 at 1. He also admitted at trial that "Allergan was attempting to avoid the compounds that were claimed in the Bito patent." D.I. 211, 313:13-16 (Woodward); *see also id*. at 317:18-21, 323:1-10. Allergan thus ignored the useful C1-amides and spent years trying to develop prodrugs by altering positions other than C1, including C9, 11, and 15, in an attempt to avoid Bito. D.I. 210, 238:4-18 (Woodward); PTX-98 at 25-27 (AGN-BAR-00244540-542); DTX-13 at 4. It also embarked on an ultimately fruitless path to developing prostaglandin "analogs," not "derivatives," in an effort to avoid the Bito patent. D.I. 211, 323:1-21 (Woodward).

Eventually, without any promising drug candidates from these other efforts, and faced with imminent competition from Pharmacia, Dr. Woodward and his colleagues thus did exactly what the prior art taught in order to compete with Pharmacia. Once Pharmacia disclosed an ester prodrug of bimatoprost free acid and other similar compounds at the 1991 ARVO conference,

Allergan turned back to the C1-amides, despite the risk of a patent infringement lawsuit. The obvious result was bimatoprost—17-phenyl $PGF_{2\alpha}$-C1 ethyl amide. Allergan's fears about doing precisely what the prior art taught and what Bito and Stjernschantz had patented were realized when Pharmacia alleged that Lumigan® infringed the Bito patent in this Court. D.I. 211, 337:4-16; *see Allergan v. Pharmacia*, No. 01-141-SLR.

Despite having had access to the above Allergan documents during more than two decades as an Allergan consultant (*see* D.I. 214, 1052:15-19, 1053:21-1054:23, 1057:6-1058:1), Dr. Macdonald ignored them and their clear support for the conclusion that bimatoprost was made as part of Allergan's *prodrug* program. *See* PTX-95 at 3-4 (AGN-BAR-00244316-317); *see also* D.I. 212, 678:18-679:13 (Wheeler). His disregard for those Allergan documents is particularly troubling given that Dr. Macdonald has been working with Allergan since 1989 on its glaucoma treatment program. D.I. 213, 995:22-996:17. His ties to Allergan's bimatoprost studies are so close, in fact, that he affirmed how "proud" he was of the role he played in the development of bimatoprost, and he even refers to the alleged "prostamide" receptor as "our receptor." D.I. 213, 1031:3-4; D.I. 214, 1055:3-20. Dr. Macdonald is thus anything but the "neutral" expert that he "hoped" would play a role in this case, and has no excuse for his decision to ignore Allergan's true bimatoprost development story. *See* D.I. 214, 1055:25-1056:3.

### E. Dr. Macdonald Agreed With The Facts Showing That The Prior Art Renders The Asserted Claims Obvious.

Dr. Macdonald agreed with all of the critical facts described above that support Defendants' position that the asserted claims are obvious:

- It was known in 1992 that bimatoprost free acid would lower IOP when administered to humans. D.I. 214, 1066:19-23 (Macdonald);
- It was undesirable in 1992 to administer bimatoprost free acid directly to the eye. *Id.* at 1064:21-1065:11, 1066:24-1067:2 (Macdonald);

- Masking the C1 carboxylic acid of that compound with a neutral moiety was known in the art. D.I. 214, 1065:19-1066:10, 1067:7-1068:6 (Macdonald);

- The Bito patent covered ester prodrugs. DTX-450 at col.16 claims 1 and 5; D.I. 213, 1014:5-8 (Macdonald); D.I. 214, 1065:19-1066:18 (Macdonald);

- Prior art prodrugs did not completely eliminate side effects like hyperemia. D.I. 214, 1091:24-1092:11 (Macdonald);

- The prior art, including the Lee & Bundgaard reference, teaches that amides could be used as prodrugs. D.I. 214, 1079:6-10 (Macdonald).

The inventors themselves confirmed that they made $PGF_{2\alpha}$ amides because they were thought to be "susceptible to metabolism, thus allowing for generation of $PGF_{2\alpha}$." DTX-13 at 4. And, not at all surprisingly, bimatoprost is useful in the treatment of glaucoma and ocular hypertension. That is precisely what the law defines as obvious. *See KSR*, 550 U.S. at 416 ("[W]hen a patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known in the field, the combination must do more than yield a predictable result"); *Eli Lilly*, 471 F.3d at 1377 (for chemical compounds, obviousness is established by demonstrating "structural similarity between claimed and prior art subject matter … where the prior art gives reason or motivation to make the claimed compositions.").

**F. Allergan Failed To Rebut This Proof Of Obviousness.**

In the face of all this, Allergan chose a trial strategy that ignored key facts establishing obviousness and focused instead on irrelevant, tangential points and secondary considerations that were never established. *See, e.g.*, D.I. 213, 1005:20-25 (Macdonald). For instance, Allergan's long-time consultant, Dr. Macdonald, criticized Defendants for referring to Compound 17 of the Stjernschantz patent as "bimatoprost free acid," D.I. 213, 1007:2-13, 1008:4-7, saying it showed Defendants improperly were applying hindsight to their obviousness analysis. *Id*. at 1007:14-15. But Dr. Macdonald ultimately admitted that he referred to the compound in the same way in his expert report and his deposition, and he did not dispute that it

accurately refers to the same prior art compound. D.I. 214, 1062:4-1064:7. Most importantly, he admitted that prior to Allergan's filing of a patent application, the compound was known in the art to be a potent agent for lowering IOP. *Id*. at 1064:9-20, 1072:13-16.

Dr. Macdonald also made much of his inability to locate the word "amide" in the Stjernschantz reference, as if that disposed of the obviousness defense. D.I. 213, 1009:18-21. It does not. He said nothing to the Court about the teaching of Stjernschantz that "various modifications of the alpha chain"—where the substitution of the amide group occurs in bimatoprost—are possible while "still using the inventive concept" disclosed. DTX-822 at 6; D.I. 212, 526:13-24 (Mitra). That, coupled with the textbook teaching that amides are suitable ocular prodrugs (DTX-1006 at 9), puts amides well within the scope of Stjernschantz's teaching.

And, while Allergan tried to make the point that both Stjernschantz and the Bito patent were before the PTO, the other art and knowledge concerning amides that Defendants cited at trial were *not* before the examiner. Allergan did not cite to the PTO Lee & Bundgaard, JP '636, or the Ho reference. They also failed to tell the examiner of the inventors' own expectation—consistent with the teachings of the art—that amides would hydrolyze and generate $PGF_{2\alpha}$ for the treatment of glaucoma in the same way the prior art esters of Stjernschantz do. The PTO has thus never considered the arguments Defendants presented at trial, and Defendants' "burden may be more easily carried" as a result. *SIBIA Neurosciences, Inc. v. Cadus Pharma. Corp.*, 225 F.3d 1349, 1355-56 (Fed. Cir. 2000).

Allergan's avoidance of substance extended to its cross-examination of Defendants' experts. Allergan made no attempt to challenge Dr. Mitra's opinions about obviousness based on the disclosures of the prior art. The cross-examination of Dr. Mitra instead focused on legally and factually irrelevant points about, for instance, the accuracy of his drawing from memory an

irrelevant portion of the bimatoprost molecule. D.I. 212, 555:20-557:13. Drawings from memory during depositions have nothing to do with the merits of the obviousness defense, such as whether the *prior art* renders bimatoprost obvious. Similarly, Allergan questioned Dr. Mitra about whether Stjernschantz disclosed statistically significant clinical results using latanoprost, a point that is not at issue in this case.[7] *See* D.I. 212, 579:11-584:8. Yet, nowhere did Allergan challenge Dr. Mitra's actual, undisputed conclusion that Stjernschantz discloses bimatoprost free acid and its efficacy in lowering IOP, prodrugs of bimatoprost free acid, and the prodrug molecule now known as latanoprost and sold as Xalatan®. In fact, Dr. Macdonald agreed that Stjernschantz made each of these important disclosures.

Allergan also attempted to attack Dr. Mitra's neutrality simply because he has testified for generic drug companies in the past. D.I. 212, 543:11-15, 547:9-12. He has no interest in bimatoprost or either of the Defendants. Moreover, Allergan makes that attack while failing to call even one witness who remotely could be considered neutral. Every witness Allergan called is either currently employed by the company or has been a paid consultant for years—decades in the cases of Drs. Macdonald and Regan. D.I. 210, 67:3-12 (Whitcup); 126:10-18 (Garst); 209:12-17 (Woodward); D.I. 212, 695:4-12 (LeCause); D.I. 213, 791:16-25 (Noecker); 900:25-902:21 (Regan); D.I. 214, 1052:15-1055:24 (Macdonald). In the end, Dr. Mitra's independent approach to the obviousness analysis was confirmed by the admissions that Dr. Macdonald could not avoid making. *See supra*, Part II.E.

## III. No Secondary Considerations Support A Conclusion Of Non-Obviousness.

Allergan tried to overcome Defendants' clear showing of *prima facie* obviousness by

[7] Defendants maintain their objection to the admissibility into evidence of PTX-1035—a prior declaration of Dr. Mitra—as hearsay. D.I. 212, 578:17-579:2; *see also, e.g.*, *Granite Partners, L.P. v. Merrill Lynch, Pierce, Fenner & Smith Inc.*, No. 96-Civ.-7874, 2002 WL 826956, at *7 (S.D.N.Y. May 1, 2002) (excluding written expert materials as "inadmissible hearsay.").

relying on alleged "secondary" considerations, including arguments about unexpected results, satisfaction of a long-felt need, copying, and commercial success. Those efforts failed. The evidence at trial established that Allergan has spent nearly 20 years trying to show that bimatoprost acts as an intact molecule on a new receptor, rather than as a prodrug, and that bimatoprost is clinically superior to the closest prior art glaucoma treatments. The overwhelming weight of the evidence proves that Allergan is wrong.

**A. Allergan Failed To Meet Its Burdens Concerning Secondary Considerations.**

Once a *prima facie* case of obviousness has been established, the burden shifts to the patentee to come forward with sufficient evidence of nonobviousness. *In re Huang*, 100 F.3d. 135, 139 (Fed. Cir. 1996). Additionally, the patentee bears the burden of establishing a nexus between the secondary considerations and the patented invention. *Crocs, Inc. v. ITC*, 598 F.3d 1294, 1310-11 (Fed. Cir. 2010); *In re GPAC*, *Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995); *In re Paulsen*, 30 F.3d 1475, 1482 (Fed. Cir. 1994).

Even if Allergan established the existence of secondary considerations and nexus, that is not enough to uphold the validity of a claim. "[A] strong *prima facie* obviousness showing may stand even in the face of considerable evidence of secondary considerations." *Rothman*, 556 F.3d at 1322; *see also Leapfrog Enters., Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007) ("[G]iven the strength of the prima facie obviousness showing, the evidence on secondary considerations was inadequate to overcome a final conclusion that [the claim] would have been obvious."); *Motorola, Inc. v. Interdigital Tech. Corp.*, 121 F.3d 1461, 1472 (Fed. Cir. 1997) ("In reaching an obviousness determination, a trial court may conclude that a patent claim is obvious, even in the light of strong objective evidence tending to show non-obviousness.").

Moreover, the rationale for giving any weight to secondary considerations is that they may "provide objective evidence of how the patented device is viewed in the marketplace, by

those directly interested in the product." *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1391 (Fed. Cir. 1988). Evidence of secondary considerations will not necessarily be relevant under that rationale, and "may in any given case be entitled to more or less weight, depending upon its nature and its relationship to the merits of the invention." *Ashland Oil*, *Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 306 (Fed. Cir. 1985).

Allergan's secondary considerations fail to establish the non-obviousness of the asserted claims under all of these standards.

**B. Bimatoprost Does Not Exhibit Any Unexpected Results.**

In an attempt to show unexpected results, Allergan suggests incorrectly that bimatoprost (1) acts as an intact amide molecule rather than as a prodrug, and (2) activates a "prostamide" receptor different from the known FP receptor on which bimatoprost free acid undisputedly acts. Both of those positions have been consistently rejected by researchers unaffiliated with Allergan. As for the intact amide molecule versus prodrug issue, the non-Allergan view as recently as 2010, is that "the only plausible explanation for the ocular hypotensive activity associated with bimatoprost is the hydrolysis to [bimatoprost free acid] by the ocular tissues . . . ." DTX-191 at 8. As for the FP receptor versus prostamide receptor issue, the non-Allergan view as recently as 2010 is that "bimatoprost acid is the active moiety acting on FP receptors to cause the IOP lowering." *Id*. Allergan provided no evidence at trial that overcomes these objective scientific conclusions.

**1. Allergan Provided No Actual Proof Of Any Unexpected, Advantageous Result.**

To show that a patented claim creates unexpected results, mere speculation or unproven hypotheses about what might become an "unexpected benefit" is not enough; there must be evidence that the benefits claimed to be unexpected *actually occur*. *See In re De Blauwe*, 736

F.2d 699, 705 (Fed. Cir. 1984) ("It is well settled that unexpected results must be established by factual evidence."); *In re Geisler*, 116 F.3d 1465, 1469 (Fed. Cir. 1997) (same); *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) (a patentee cannot prove unexpected benefits with "bare statements without objective evidentiary support."); *In re Vamco Mach. & Tool*, 752 F.2d 1564, 1577 (Fed. Cir. 1985); *In re Klosak*, 455 F.2d 1077, 1080 (C.C.P.A. 1972) ("Nor is it enough to show that certain results would not have been expected by those skilled in the art without establishing that those results are actually obtained through one's invention.").

Even if one can make a threshold showing that an unexpected result exists, it remains irrelevant to obviousness unless and until it is shown to cause an unexpected benefit when compared to the prior art. *In re Geisler*, 116 F.3d at 1469 (Fed. Cir. 1997) (patentee must "show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected."); *see also In re De Blauwe*, 736 F.2d at 705 (unexpected "results must logically be shown as superior *compared* to the results achieved with other [prior art inventions].") (emphasis in original). Even then, if a "'modification results in great improvement and utility over the prior art, it may still not be patentable if the modification was within the capabilities of one skilled in the art . . . .'" *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004) (quoting *Huang*, 100 F.3d at 139).

Allergan cannot overcome the clear obviousness of its patents in view of this framework and the facts established at trial.

**a. Bimatoprost Is A Prodrug.**

The evidence discussed above establishes that it was obvious to make an amide form of known bimatoprost free acid, and that those compounds would be reasonably expected to result

in a successful treatment for glaucoma. Allergan effectively admits that this was the *expected* result when it argues that bimatoprost is *not* a prodrug and that this is the *unexpected* result. In any event, Allergan's theory is unsupported by the evidence.

**i. Bimatoprost Hydrolyzes Into Bimatoprost Free Acid.**

Allergan admitted at trial that the administration of its commercial embodiment, Lumigan®, results in the formation of bimatoprost free acid in the eye. *See, e.g.*, D.I. 210, 101:23-102:3 (Whitcup); D.I. 211, 359:20-23 (Woodward); D.I. 212, 669:13-19 (Chen); *id*. at 689:19-25 (Wheeler); D.I. 213, 921:5-8 (Regan). The only dispute Allergan tried to manufacture was whether the amount of free acid formed is sufficient to cause its IOP-lowering effect. *See, e.g.*, D.I. 214, 1077:7-10 (Macdonald); D.I. 210:, 254:23-255:2 (Woodward). The most relevant evidence—that is, studies examining hydrolysis of bimatoprost in live human eyes—confirms that Allergan's argument is incorrect. *Every single study* conducted to date in human ocular tissues from live patients establishes that bimatoprost undergoes hydrolysis into its free acid in an amount sufficient to account for the IOP-lowering effects of Lumigan®.

The first such study was conducted in 2004 by Dr. Carl Camras, who concluded "that bimatoprost is a prodrug that is hydrolyzed to its free acid, achieving sufficient concentrations in the aqueous humor to activate the FP prostanoid receptor and to reduce IOP . . . ." DTX-235 at 5; D.I. 213, 928:12-20 (Regan). Allergan's expert, Dr. Regan, acknowledged that Dr. Camras was a "very well-respected," "[v]ery important figure to the scientific development of drugs to treat glaucoma." D.I. 213, 922:9-21. Even Dr. Woodward testified that he would not expect Dr. Camras's data "to be faulty." D.I. 211, 362:7-18.

As recently as 2010, another group of researchers performed similar experiments to those of Dr. Camras and concluded even more emphatically that "the *only plausible explanation* for

the ocular hypotensive activity associated with bimatoprost is the hydrolysis to [bimatoprost free acid] by the ocular tissues and the activation of the FP receptors by the resultant [bimatoprost free acid.]" DTX-191 at 8 (emphasis added). At least seven other studies have reached the same conclusion, either with live human patients, human ocular tissues, or in animal models. *See* DTX-439 at 2-3 (discussing other *in vivo* or *in vitro* human and animal models supporting the conclusion that bimatoprost is a prodrug).

The only paper even hinting at a different conclusion based on data from live human eyes is the Cantor paper, co-authored by Dr. Woodward and Dr. Wheeler, Allergan's Senior Vice President of Biological Sciences. PTX-225. This paper timidly concludes that the data is "consistent with a hypothesis that bimatoprost is not a prodrug . . . ." *Id*. at 5 (AGN-BAR-01004929). At the same time, however, the authors admit that the numbers they report *underestimate* the amount of bimatoprost free acid found in the tested patients. *Id*. Moreover, they misinterpreted the underestimated data they did report. As Dr. Camras wrote after reviewing that study:

> [The Allergan scientists] appear to reach conclusions that are not supported by their own data…..The *key and unambiguous observation* that we believe is critical is that, no matter what values were obtained *in each and every study, all of the concentrations*, including the lower concentrations of the free acid of . . . [bimatoprost] found by [the Allergan scientists], *are high enough to account for their activity at FP prostanoid receptors*.

DTX-439 at 2 (emphasis added).

Allergan's evidence from other sources fared no better at trial. Allergan showed the Court Dr. Woodward's conclusion in 2001 that "bimatoprost is not converted to the free acid in human eyes." PTX-495A at 8 (AGN-BAR-02159818). But Allergan's own expert testified that this conclusion was "incorrect." D.I. 213, 921:2-8 (Regan). Indeed, Dr. Woodward's conclusion was unequivocally contradicted by the live human studies performed by Dr. Camras and others,

including Dr. Woodward's own data from the Cantor paper that *did* show hydrolysis of bimatoprost into its free acid. DTX-235 at 5; DTX-191 at 7-8; PTX-225 at 3 (AGN-BAR-01004927).

**ii. FDA's Center For Drug Evaluation And Research Concluded In 2010 That Bimatoprost Is A Prodrug.**

The FDA's Center for Drug Evaluation and Research ("CDER") also weighed in on the issue as recently as August 2010 and reached the same conclusions. DTX-1123 at 23 (AGN-BAR-02153790). That neutral agency is charged with the scientific review and evaluation of technical drug data within the FDA's jurisdiction, including Lumigan®. It is a department distinct from the Division of Drug Marketing, Advertising, and Communications ("DDMAC"), the FDA division Allergan attacked as being concerned with advertising, not scientific issues. *See, e.g.*, D.I. 210, 85:1-12, 86:18-87:1 88:25-89:6, 91:5-8, 104:18-105:19 (Whitcup). The Director of the CDER, Dr. Janet Woodcock, had access to all of the published literature and concluded that "[t]here is much stronger evidence based on both animal and human studies that Xalatan, *Lumigan*, and Travatan are *pro-drugs* that are converted to the free acid form in the ocular tissue, and the free acid form of the drugs acts upon prostaglandin receptors (the amide group is absent when the Lumigan molecule acts upon the prostaglandin receptor)." DTX-1123 at 23 (AGN-BAR-02153790) (emphases added). The FDA's conclusion on these points—based on the unique scientific expertise of the CDER—is entitled to considerable deference from the Court. *Somerset Pharms., Inc. v. Shalala*, 973 F. Supp. 443, 453 (D. Del. 1997) ("[T]he FDA is to be accorded deference when it is evaluating scientific data within its technical expertise . . . ."); *Marsh v. Ore. Natural Res. Council*, 490 U.S. 360, 376-377 (1989) (In regards to "a factual dispute the resolution of which implicates substantial agency expertise . . . . [a court] must defer to 'the informed discretion of the responsible federal agencies.'") (quoting *Kleppe v. Sierra Club*,

427 U.S. 390, 412 (1976)).

**b. Bimatoprost Does Not Activate A New Receptor Different From The Known FP Receptor.**

Allergan also tried to invoke at trial the existence of hypothetical "prostamide" receptor. Its theory is that any intact amide bimatoprost remaining in the eye after Lumigan® hydrolyzes into the free acid may lower IOP by activating the hypothetical prostamide receptor, which is allegedly different from the known FP receptor that responds to $PGF_{2\alpha}$, bimatoprost free acid, and all other $PGF_{2\alpha}$ derivatives. But Allergan presented the Court with no reason to ignore the clear evidence presented at trial that Allergan's theory is incorrect.

Allergan admits there is a dispute in the scientific community about this issue. D.I. 212, 687:22-24 (Wheeler); D.I. 213, 851:1-9 (Noecker); *id*. at 904:8-18, 907:1-16 (Regan). But it is hardly a dispute. With the exception of those working for or with Allergan, *every* scientist to have performed independent studies on the issue—including the FDA's CDER—concludes that the "prostamide" receptor theory is wrong, and that bimatoprost acts in its free acid form on the known FP receptor. *E.g.*, DTX-235 at 5 ("Because a sufficient concentration of a known FP agonist [i.e., bimatoprost free acid] is achieved in aqueous humor with bimatoprost therapy, postulation of the existence of a novel receptor to account for its mechanism of action is not required."); DTX-191 at 8 ("[T]he majority of published evidence indicates that bimatoprost amide is a PG prodrug that liberates the FP agonist BFA . . . and thus bimatoprost acid is the active moiety acting on FP receptors to cause the IOP lowering."); DTX-1123 at 23 (rejecting the Allergan hypothesis that "Lumigan effects appear independent of prostanoid FP receptor activation"). Allegan did not bring any independent witnesses to trial to refute that conclusion, and is still publishing research trying (unsuccessfully) to change the prevailing view. *See* DTX-337; D.I. 211, 372:18-373:6 (Woodward).

Dr. Regan—yet another long-term Allergan-paid consultant who was presented by Allergan at trial as a neutral witness—even admitted that the "prostamide" receptor has never been shown to exist naturally in any human tissues, let alone any ocular tissues relevant to lowering IOP.[8] D.I. 213, 900:25-902:21, 955:13-956:12; *see also* D.I. 214, 1132:20-1133:5 (Sherman). In fact, three years after the publication of Dr. Woodward's alleged molecular cloning data, the scientific community outside of Allergan still does not recognize the existence of a prostamide receptor separate and distinct from the FP receptor. *E.g.*, DTX-1123 at 23 (AGN-BAR-02153790) (FDA's CDER, 2010: noting that Allergan's "hypothesis implies the existence of a novel prostanoid receptor that has never been characterized."); DTX-191 at 8. Even the International Union of Basic and Clinical Pharmacology has granted *only* that the existence of a "prostamide" receptor "has been proposed." PTX-971 at 4. The only person who proposed it was Dr. Woodward. D.I. 211, 380:13-17, 382:20-383:2 (Woodward).

Dr. Sherman's testimony summarizes the state of the scientific evidence on this issue: "So far, none of the data that has been presented by Allergan shows the physical existence of the receptor itself." D.I. 214, 1163:6-8. Allergan did not cross Dr. Sherman on this, but instead devoted its questioning to wholly irrelevant points. For instance, Allergan questioned him about what tests he might have conducted to prove the existence or non-existence of the prostamide receptor since being retained as an expert in this case, while ignoring the fact that neither Dr. Woodward nor Allergan has done that same testing in the nearly twenty years since filing the patent application. *E.g.*, D.I. 214, 1161:9-1163:25, 1170:23-1174:18. Allergan then inquired about Dr. Sherman's hands-on experience cloning GPCRs, presumably because Allergan had no basis for attacking his opinions about what all the available literature on the topic—including

[8] Defendants object to the testimony of Dr. Regan concerning the hypothesized "prostamide receptor" for the reasons set forth in their *Daubert* motion. *See* D.I. 184, 185, 201.

publications by Dr. Regan—suggests: bimatoprost acts through its free acid on the known FP receptor. *See id*. at 1177:19-1178:9 (Sherman). At no time did Allergan attempt to substantively challenge Dr. Sherman's opinion that bimatoprost is a prodrug that activates the known FP receptor.

Furthermore, assuming *arguendo* that a prostamide receptor does exist, the record confirms it would function exactly like the known "classical" FP receptor. Allergan at most claims to have discovered that the prostamide receptor is a "splice variant" of the classical FP receptor. That splice variant is hypothesized to be a truncated version of the classical FP receptor, and the two come from the same gene. D.I. 214, 1127:11-23 (Sherman); D.I. 213, 952:15-17 (Regan). There is no dispute, however, that this splice variant is, at most, a "dead, non functional" protein in the absence of the classical FP receptor. PTX-221A at 6 (Fig. 4(c)(I)-(II)), 13 (AGN-BAR-02159801, AGN-BAR-02159808); D.I. 214, 1129:13-15 (Sherman); D.I. 213, 952:18-953:6 (Regan); *see also* D.I. 214, 1124:9-1125:20, 1128:2-20 (Sherman); DTX-1015 at 1. Allergan's data also confirms that when this alleged splice variant functions together with the known FP receptor, the resulting activity is identical to that of the known FP receptor. *See, e.g.*, PTX-221A at 6 (Fig. 4(a), (b)) (AGN-BAR-02159801); D.I. 213, 953:8-954:11 (Regan); D.I. 214, 1131:4-12 (Sherman). It is thus not surprising that Dr. Regan agreed that other known prostaglandins, like $PGF_{2\alpha}$, activate the alleged splice variant prostamide receptor. D.I. 213, 953:16-954:3; *see also* D.I. 214, 1131:4-22 (Sherman). He also admitted that bimatoprost free acid would activate the elusive prostamide receptor, as would latanoprost's active form and other prostaglandin analogs. D.I. 213, 954:4-22. Simply put, there would be nothing unique, surprising, or unexpected about the "prostamide" receptor if it did exist.

All of these facts also make Allergan's "unexpected results" theory legally irrelevant.

There is not a single document or statement from any witness suggesting a benefit or advantage resulting from the alleged inherent activity of bimatoprost or the "prostamide" receptor. They would be at most distinctions without a difference, and would not provide evidence of non-obviousness under controlling law. *In re Geisler*, 116 F.3d at 1469 (an unexpected result must exhibit "some superior property or advantage" compared to the prior art.). Allergan made no suggestion at trial that the allegedly unique "non-prodrug" and "prostamide" receptor theories result in any of the alleged clinical differences between bimatoprost and any other prior art drug. Any such suggestion would fail because, as discussed below, bimatoprost has no clinically superior aspects relative to any other prostaglandin marketed for the treatment of glaucoma. *See infra*, Part III.C.

**2. There Is No Nexus Between These Alleged Results And The Asserted Claims.**

It is also noteworthy that Allergan's 1992 patent filing and the patents-in-suit do not actually claim a compound that acts on a novel receptor or by any different mechanism from the prior art compounds, a fact Dr. Woodward reluctantly admitted. JTX-1 at col.14 claims 1-3; JTX-3 at cols.14-15 claim 10; D.I. 211, 294:15-17, 295:12-16, 296:11-18, 309:20-310:8. It would have been impossible to claim those aspects because, as Dr. Woodward also admits, the structure of the hypothetical "prostamide" receptor was not even known to Allergan when the patents issued (nor is it known today). *Id*. at 310:2-8; *see also id*. at 291:8-11. Allergan's focus on these unclaimed "unexpected" results is thus legally irrelevant because no connection exists between those allegations and the claims at issue. *Demaco*, 851 F.2d at 1392 (noting that it is the patentee's burden to show a "legally and factually sufficient connection between the [secondary consideration] and the *patented invention*") (emphasis added).

Nearly 20 years after the first patent filing in this case, the existence of the alleged

unexpected properties of bimatoprost is still in dispute outside of the courtroom, with Allergan pitted against the rest of the scientific community. Allergan's lack of evidence and sheer speculation in this regard cannot overcome Defendants' *prima facie* showing of obviousness.

### C. Bimatoprost Is Not Superior To Other Prior Art Prostaglandin Glaucoma Treatments.

Allergan and its clinical expert, Dr. Noecker—the third of Allergan's "neutral" experts and the third to have worked for the company for years before this litigation (D.I. 213, 791:16-25)—also argued that bimatoprost and Lumigan® are more efficacious than prior art drugs, such as Xalatan® (latanoprost, or Compound 9 of Stjernschantz). That argument is directly contrary to what Allergan has told and continues to tell ophthalmologists outside the courtroom: "Lumigan® should ***not*** be considered as having superior IOP lowering efficacy compared to other medications . . . ." PTX-222 at 1 (AGN-BAR-00940949) (emphasis added); *see also* PTX-219. The evidence established at trial is consistent with Allergan's admission.

#### 1. Bimatoprost Is In The Same Class, And Has The Same Mechanism of Action, As The Prior Art.

Bimatoprost and latanoprost belong to the same class of drugs, called prostaglandin analogs. PTX-342 at 1 (AGN-BAR-02080385) (describing bimatoprost as "a synthetic structural analog of prostaglandin"); PTX-564 at 3 (Barr_Bimat000019) (same); PTX-760 at 1 (Barr_Bimat156069) ("Latanoprost is a prostaglandin $F_{2\alpha}$ analogue."); PTX-792 at 1 (SAND-BIMA 001518) (describing bimatoprost as a "synthetic structural analog of prostaglandin"). Both drugs also have the same mechanism of action, which is lowering intraocular pressure by increasing outflow of aqueous humor. *See, e.g.*, *id.*; D.I. 210, 100:13-15 (Whitcup); D.I. 211, 462:15-18 (Mitra); D.I. 214, 1188:13-18 (Wright). The parties are even in agreement about how the drugs do that. Lumigan® and Xalatan® both increase outflow through separate areas of the eye called the uveoscleral pathway and the trabecular meshwork. D.I. 213, 850:8-25 (Noecker);

D.I. 210, 118:6-18 (Whitcup); DTX-304 at 1; D.I. 211, 359:11-18 (Woodward).

**2. Clinical Studies Demonstrate That Lumigan® Does Not Have Superior Efficacy Over The Prior Art.**

Studies of the effectiveness of bimatoprost and latanoprost in real-world patients unanimously conclude not only that bimatoprost is not superior to latanoprost, but that *latanoprost* may even "lead to better control of intraocular pressure . . . ." DTX-1024 at 1; D.I. 213, 797:19-798:6 (Noecker); *see also* DTX-1026 at 2 ("Patients were more persistent with latanoprost and demonstrated lower intraocular pressure . . . when compared to bimatoprost . . . ."); DTX-1025 at 7 ("[L]atanoprost, bimatoprost and travoprost are comparable in their IOP-lowering abilities."). Data from more controlled clinical studies also supports the conclusion that bimatoprost does not have superior efficacy compared to latanoprost. *E.g.*, PTX-532 at 1 ("Latanoprost, bimatoprost, and travoprost were comparable in their ability to reduce IOP in [glaucoma] patients."); DTX-1019 at 6 (comparing the efficacy of latanoprost, bimatoprost, and travoprost and concluding that there is "equivalence across all three included drugs.").

None of the evidence Dr. Noecker relied on in forming his conclusion contradicts these findings. He only suggested that—while purposely avoiding any details—there were a number of head-to-head clinical studies supporting the opinion that "Lumigan lowers eye pressure better than Xalatan." D.I. 212, 765:25-766:12. The only one he actually showed the Court was his own Allergan-funded study. PTX-528; D.I. 212, 766:13-22. That study concluded that the average difference in IOP-lowering between bimatoprost and latanoprost was less than two millimeters of mercury. D.I. 212, 768:19-769:10 (Noecker); PTX-528 at 1 (AGN-BAR-02156043) (Results). But that range is within the plus or minus one millimeter of mercury that Dr. Noecker himself said is the standard of error inherent in the device used to measure IOP. D.I. 213, 827:15-828:10. It is also within the error range of *three* millimeters that Dr. Noecker

can see once or twice a day in his own practice. D.I. 213, 814:9-18; *see also* DTX-1124 at 1 (noting "sources of error which significantly influence" readings on the Goldmann tonometer). When accounting for these error ranges, Dr. Noecker's own self-described "excellent" study shows no difference at all between bimatoprost and latanoprost.

Consistent with its strategy of avoiding the substantive issues, Allergan also cites Barr's ANDA to support its clinical superiority theory. But it ignored that the entire purpose of an ANDA filing is to demonstrate bioequivalence with a brand product without having to undertake independent research about product background. In line with that understanding, the ANDA statements cited by Allergan at trial are taken directly from Allergan publications:

| Statements In Barr's ANDA (PTX-570) | Direct Quotes From Allergan Publications |
|---|---|
| PTX-570 at 9: "Bimatoprost is clinically the most efficacious ocular hypotensive agent and its activity exceeding that of both timolol and latanoprost." | DTX-985 at 2: "Bimatoprost is . . . clinically the most efficacious ocular hypotensive agent reported to date, its activity exceeding that of both timolol and latanoprost." |
| PTX-570 at 9: "Studies have revealed that unlike latanoprost, bimatoprost is not significantly metabolized, because of the absence of free acid hydrolysis product in systemic circulation after topic ocular administration to human volunteers." | PTX-468 at 2 (AGN-BAR-02154708): "[S]tudies with bimatoprost reveal that, unlike latanoprost, bimatoprost is not significantly metabolized due to the absence of free acid hydrolysis product in systemic circulation after topical ocular administration to human volunteers." |

That is exactly what would be expected of an ANDA applicant trying to demonstrate bioequivalence, and there is no evidence that Barr's statements were the result of an independent analysis of the scientific literature. Barr's reference to Allergan's own claims regarding Lumigan® does nothing to address the scientific flaws in Allergan's theories, and ultimately is just another attempt to emphasize irrelevancies and avoid their scientifically rejected conclusions.

### 3. The Alleged Existence of Xalatan® "Non-Responders" Does Not Support A Conclusion Of Non-Obviousness.

Dr. Noecker's opinions about the use of bimatoprost in patients who respond less well to latanoprost are also fundamentally flawed. To the extent Allergan tries to argue these opinions are somehow relevant to satisfaction of a long-felt but unmet need (it has not done so), the relevant evidence must have "*existed* on the patent's filing date" to be considered a secondary consideration of nonobviousness. *Perfect Web Tech., Inc. v. InfoUSA, Inc.*, 587 F.3d 1324, 1332 (Fed. Cir. 2009) (emphasis added); *see also Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 998 (Fed. Cir. 2009) ("[W]e look to the filing date of the challenged invention to assess the presence of a long-felt and unmet need."). Each and every one of the studies Dr. Noecker relied on in opining that Lumigan® is a more effective treatment for so-called Xalatan® non-responders is thus irrelevant because they all post-date the invention date by at least nine years. *See* PTX-215 (2004); PTX-476 (2002); PTX-486 (2003); PTX-501 (2001); PTX-504 (2003); PTX-505 (2001); PTX-509 (2008); PTX-527 (2001); PTX-528 (2003); PTX-535 (2002).

Not only must the need exist and be recognized as of the filing date, but the alleged invention must also be recognized as a solution to the problem. *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 884 (Fed. Cir. 1998) ("[I]t is difficult to see how a solution solves long-felt need if its developer does not recognize that it does so."). Allergan offered no evidence that anyone recognized a "non-responder" problem or that use of the bimatoprost compound would have solved it during the relevant 1992 timeframe. The purported need did not even exist in 1992—Xalatan® was not marketed until 1996, and Lumigan® was not marketed until 2001. D.I. 212, 700:22-25 (LeCause).

Dr. Noecker in any event offered insufficient facts to support his conclusion that bimatoprost is more effective in certain patient groups who are less responsive to latanoprost.

While he refused to make a "totally definitive conclusion" from studies that tested 64 patients or less when those conclusions would be contrary to his opinions, he had no problem relying on a study involving only 15 patients to support his opinion that bimatoprost functions effectively in Xalatan® "non-responders." PTX-486 at 1; D.I. 213, 824:5-8; D.I. 212, 764:3-13; PTX-476 at 6 (AGN-BAR-02154817) (21 patients); D.I. 212, 763:2-16; *see also* D.I. 214, 1205:13-1206:10, 1206:20-1207:3 (Wright). Much of the data on which Dr. Noecker relies is therefore inconclusive at best. He also admitted that "Xalatan non-responder" can be defined in "a lot of different ways," though such definitional variance was not controlled for in any of the studies on which he relied. D.I. 213, 844:25-845:3; *see also* D.I. 214, 1189:16-1190:11 (Wright). Some of these same studies were also flawed because they were open-labeled studies that did not adequately control for bias. *E.g.*, PTX-504 at 1; PTX-476 at 3 (AGN-BAR-02154814); D.I. 214, 1206:11-18, 1206:20-1207:3 (Wright). It is not surprising in view of this flawed data that the FDA *again* blocked Allergan from "misleadingly" claiming that "Lumigan will be effective after latanoprost stops working or when latanoprost is no longer effective in adequately lowering [IOP] . . . ." DTX-1113 at 2.

Allergan and Dr. Noecker also failed to account for at least two alternative explanations for bimatoprost's activity in these patients that are both unrelated to any allegedly unpredictable differences between the molecules. The first relates to dosing differences. All of the studies presented at trial involved commercial doses of Lumigan® (.03% bimatoprost) and Xalatan® (.005% latanoprost). D.I. 213, 845:22-846:6 (Noecker). This means Lumigan® patients automatically received six times more active drug than Xalatan® patients. *Id*. Yet, no head-to-head study has ever been conducted using equal concentrations of the active ingredients. *Id*. at 846:10-847:6 (Noecker). Any observed differences between the activity of Lumigan® and

Xalatan® may therefore be due simply to differences in their concentrations. *See id*. at 852:17-854:8 (Noecker); D.I. 214, 1207:12-1208:7 (Wright).

As another alternative explanation, bimatoprost may be more effective in certain latanoprost patients because those patients produce insufficient esterase enzymes to hydrolyze the latanoprost ester into its active free acid. D.I. 213, 847:7-13 (Noecker); D.I. 214, 1146:15-22 (Sherman), *id*. at 1207:12-1208:3 (Wright). The authors of one of the papers Dr. Noecker relied on recognized this possibility, suggesting that "the lack of response to latanoprost in our patient population might also involve poor deesterification of the prodrug to the pharmacologically active free fatty acid." PTX-486 at 3-5. That these patients may still have the appropriate amidase enzymes to hydrolyze bimatoprost into bimatoprost free acid would not have been surprising to a person of ordinary skill in 1992. D.I. 214, 1147:3-13 (Sherman).

Ultimately, Allergan offered only self-serving testimony from Dr. Noecker and conclusory assertions that are insufficient to legally establish clinical superiority. That is particularly true in a case such as this, where Allergan's expert agrees there is no unanimity in the ophthalmology community concerning the relative efficacy of the alleged invention and prior art compounds. D.I. 213, 817:23-819:1 (Noecker).

**D. Allergan Did Not Meet Its Burden On Satisfaction Of Any Long-Felt Need.**

Dr. Noecker also briefly offered testimony concerning bimatoprost's alleged satisfaction of a generalized "long-felt but unmet need." D.I. 212, 777:8-778:12. To the extent Allergan suggests arguments about clinical efficacy are relevant to that need (it has not done so), the argument that bimatoprost "satisfied" any unmet need fails for the reasons stated above in connection with Allergan's clinical superiority arguments. *See supra*, Part III.D. Even if it was somehow superior, that is still insufficient to establish satisfaction of a long-felt need. In the context of drugs for use in human therapy (as in this case), a "long-felt but unsolved need" is not

present where there are already several other effective drugs of the same class in the marketplace. *See Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, No. 2:05-CV-421, 2006 WL 2008962, at *45 (E.D. Va. July 17, 2006) (finding that there is "simply no 'long-felt need'" for a drug where there were "several effective" drugs of the same class already on the market), *rev'd on other grounds*, 499 F.3d 1293 (Fed. Cir. 2007). That is true in this case, where the drug alleged to have satisfied the need sells less than half as much as the prior art drug marketed as Xalatan®. PTX-994 at 5; *see also* D.I. 212, 730:4-731:17 (LeCause).

Dr. Noecker's opinions should also be disregarded for two additional reasons. First, he failed to provide a basis for opining about the existence or characteristics of an alleged long-felt need in his expert report. D.I. 212, 777:13-17.[9] His testimony on this topic should therefore be stricken. Court's Guidelines for Civil Trials at 3.

Second, even if the Court considers this testimony, Dr. Noecker failed to establish that there *was* a long-felt need to be satisfied. The Federal Circuit has made clear that establishing long-felt need requires a showing of the time when the problem first arose; a description of the problem; evidence concerning previous efforts to solve the problem; the length of time the need for a solution was felt; and alleviation of the long-felt, unmet need by the patented invention. *See Perfect Web*, 587 F.3d at 1332 ("[Plaintiff] fails to show that these drawbacks constituted a long-felt, unmet need alleviated by the patent. [Plaintiff] provided no evidence to explain how long this need was felt, or when the problem first arose."); *Tex. Instruments, Inc. v. U.S. ITC*, 988 F.2d 1165, 1178 (Fed. Cir. 1993) ("[L]ong-felt need is analyzed as of the date of an articulated identified problem and evidence of efforts to solve that problem.").

Dr. Noecker did not establish any of those things. The entirety of his testimony about

[9] This issue is addressed more fully in Defendants' pending *Daubert* motion to exclude Dr. Noecker's testimony on the topic of long-felt need (D.I. 186, 187, 201).

what the problem was or how long it had been felt consisted of the vague, conclusory statement that "at the time [Lumigan®] came to market, there was—there was still a considerable number of patients who were not well controlled, which in turn meant that they were losing vision." D.I. 212, 777:9-12. He said nothing about how long the need had been felt, what the "considerable" number of patients was, or what it means that these alleged patients "were not well controlled." Nor does he provide any meaningful testimony about what efforts were taken to try to treat these patients. He suggested only that an unidentified group of drugs was unable to treat an unidentified group of patients. *Id*. at 777:21-25. Dr. Noecker then provided only conclusory statements about being able to "effectively treat" (without any explanation as to what that means) another unidentified number of patients. *Id*. at 778:1-12. That sparse testimony fails to establish the existence of a long-felt need or that Lumigan® could have satisfied it.

**E. "Copying" Does Not Support Non-Obviousness In Hatch-Waxman Cases.**

Allergan also suggests that Defendants allegedly copied the claimed compound. That argument must fail in this ANDA case. Evidence that a generic pharmaceutical company filed an ANDA to make a bioequivalent version of a plaintiff's brand drug is not compelling evidence of a secondary consideration supporting non-obviousness. *Purdue Pharma Prods. L.P. v. Par Pharm., Inc.*, 377 F. App'x 978, 983 (Fed. Cir. 2010) ("[W]e do not find compelling [Plaintiff's] evidence of copying in the ANDA context where a showing of bioequivalency is required for FDA approval."); *see also Purdue*, 642 F. Supp. 2d at 373 ("A showing of copying . . . is not compelling evidence of non-obviousness in the Hatch-Waxman context.").

**F. Lumigan® Is Not A "Commercial Success."**

Allergan finally argues that bimatoprost is not obvious because Lumigan®, the worst selling of the three prostaglandin glaucoma treatments currently on the market, is a "commercial success" indicative of non-obviousness. The record does not support that conclusion.

A patentee offering evidence of "commercial success" to support nonobviousness bears the burden of showing that there was, in fact, commercial success, and that any such success is attributable to the claimed invention rather than to other, unrelated factors. *In re Paulsen*, 30 F.3d at 1482. One factor relevant to the commercial success inquiry is the displacement of other products' market share. *See Cable Elec. Prods., Inc. v. Genmark, Inc.*, 770 F.2d 1015, 1026-27 (Fed. Cir. 1985), *rev'd on other grounds*, *Midwest Indus., Inc. v. Karavan Trailers, Inc.*, 175 F.3d 1356 (Fed. Cir. 1999); *Kansas Jack, Inc. v. Kuhn*, 719 F.2d 1144, 1151 (Fed. Cir. 1983). The Federal Circuit has also made clear that sales figures alone are not compelling evidence of commercial success absent context to the figures. *Purdue*, 377 F. App'x at 983.

As evidence of commercial success, Allergan offered the non-expert testimony of Mr. LeCause, yet another Allergan-employed witness who has only two years of marketing experience limited solely to Allergan's Alphagan® product. D.I. 212, 697:22-698:6; 719:8-23. Yet, Allergan ignored the appropriate legal standards. Mr. LeCause instead relied on raw sales figures and vague, conclusory statements about the alleged "financial[] success" of Lumigan®. D.I. 212, 704:24-25, 709:5-11 (LeCause). He did not try to discuss or evaluate the context of the full market or the comparative sales achieved by the other prostaglandin drug products. *Id*. at 731:3-11. Defendants' expert, Mr. Boghigian, did do that. Based on those considerations, he arrived at the conclusion that Lumigan® was viewed by the market as a non-inventive "me too" drug, the raw sales of which say nothing about whether it would have been obvious to make. D.I. 214, 1230:9-22, 1240:21-25 (Boghigian). Allergan's own internal documents demonstrate that Lumigan's growth and adoption over the first sixty-five weeks of its launch were slow and flat. D.I. 214, 1232:18-1233:13 (Boghigian); DTX-405 at 132. That is in stark contrast with Xalatan®—the first prostaglandin glaucoma treatment to be marketed, years before Allergan's

patents even issued—which showed extremely rapid market uptake when launched. *Id*. After nearly ten years on the market, Lumigan® is still prescribed at less than half the rate of latanoprost, and holds third place among three competitors. D.I. 214, 1233:14-1234:8 (Boghigian); D.I. 212, 730:4-14 (LeCause); PTX-994.

Far from indicating a novel treatment, the sales figures and market position associated with Lumigan® reflect only that Allergan made an obvious decision to make an obvious prostaglandin analog that could ride the coattails of latanoprost, an identically classed and equally effective prior art drug.

## IV. Claim 10 of The '819 Patent Is Invalid Under 35 U.S.C. § 112, ¶ 4.

Finally, dependent Claim 10 of the '819 patent is invalid under 35 U.S.C. § 112, ¶ 4 if the Court agrees that the claim term "$–N(R^4)_2$" means that the two $R^4$ groups must be identical.[10]

Section 112, ¶ 4 states that "a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed." This means that if a dependent claim (here, Claim 10) is outside the scope of an independent claim (here, Claim 5), it is invalid because it fails to "specify a further limitation of the subject matter." *See Pfizer, Inc. v. Ranbaxy Labs. Ltd.*, 457 F.3d 1284, 1291-92 (Fed. Cir. 2006). The *Pfizer* decision is illustrative. The court there addressed the validity of claim 6 of the relevant patent, which depended from claim 2. *Id*. It was undisputed that claim 2 was limited to an acid of the compound at issue, while claim 6 expressly included salts of the compound. *Id*. at 1291. The defendant thus argued that claim 6 did not "specify a further limitation of the subject matter" claimed in claim 2. *Id*. The court agreed, holding the claim invalid under § 112, ¶ 4. *Id*.

The same holding must apply here. Dependent Claim 10 specifically recites and includes

[10] Properly construed, the limitation "$–N(R^4)_2$" contained in Claim 10 of the '819 patent means that both $R^4$ elements are identical. Bimatoprost does not meet this limitation. Defendants addressed claim construction issues more fully in their *Markman* briefs. (D.I. 155, 164).

the chemical name of bimatoprost: cyclopentane N-ethyl heptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1,2,3,5]. At the same time, it is undisputed that under Defendants' proposed claim construction—i.e., the two $R^4$ groups in the claim term "$N(R^4)_2$" are identical—bimatoprost is outside the scope of independent Claim 5 (as well as Claim 10) because bimatoprost does not contain identical $R^4$ groups. D.I. 211, 421:9-423:1, 430:4-11 (Macdonald). Thus, if the Court adopts Defendants' proposed claim construction, then Claim 10 of the '819 patent is invalid under § 112, ¶ 4. *Pfizer*, 457 F.3d at 1292. Any argument by Allergan that a claim could be saved simply by re-writing it in independent form is too little, too late, because courts "'should not rewrite claims to preserve validity.'" *Id*. (quoting *Nazomi Comm.'s, Inc. v. Arm Holdings, PLC*, 403 F.3d 1364, 1368 (Fed. Cir. 2005)).

**CONCLUSION**

For all the reasons stated above, Defendants respectfully request that this Court find the '819 and '649 patents invalid under 35 U.S.C. § 102, § 103, and § 112, and that Defendants' products do not infringe the '819 patent.

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Respectfully submitted,

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