NOTE: This disposition is nonprecedential.

United States Court of Appeals for the Federal Circuit

ALLERGAN, INC.,
Plaintiff-Appellee,

v.

BARR LABORATORIES, INC.,
TEVA PHARMACEUTICALS USA, INC.,
AND TEVA PHARMACEUTICAL INDUSTRIES LTD.,
Defendants-Appellants,

AND

SANDOZ INC.,
Defendant-Appellant.

2012-1040, -1054

Appeals from the United States District Court for the District of Delaware in No. 09-CV-0333, Judge Sue L. Robinson.

Decided: January 28, 2013

JONATHAN E. SINGER, Fish & Richardson, P.C., of Minneapolis, Minnesota, argued for plaintiff-appellee.

With him on the brief were DEANNA J. REICHEL; and JUANITA R. BROOKS, of San Diego, California; and DOUGLAS E. MCCANN, of Wilmington, Delaware. Of counsel on the brief was JEFFREY T. THOMAS, Gibson, Dunn & Crutcher LLP, of Irvine, California.

MEREDITH MARTIN ADDY, Steptoe & Johnson, LLP, of Chicago, Illinois, argued for defendants-appellants. With her on the brief for Sandoz, Inc. were THOMAS J. FILARSKI and BRANDON C. HELMS. On the brief for Barr Laboratories, Inc., et al, were GEORGE C. LOMBARDI and BRADLEY C. GRAVELINE, Winston & Strawn, LLP, of Chicago, Illinois.

Before RADER, *Chief Judge*, BRYSON,[*] and WALLACH, *Circuit Judges*.

WALLACH, *Circuit Judge*.

Barr Laboratories, Inc., Teva Pharmaceuticals USA, Inc., and Teva Pharmaceutical Industries Ltd. (collectively, "Barr"), and Sandoz Inc. ("Sandoz") appeal from the decision of the United States District Court for the District of Delaware, which held that Barr's and Sandoz's proposed products (described in Abbreviated New Drug Applications ("ANDA") Nos. 91-194 and 200487, respectively) infringed claim 10 of Allergan, Inc.'s ("Allergan") U.S. Patent No. 5,688,819 ("the '819 patent") and that the asserted claim was not invalid.[1] *Allergan, Inc. v. Barr*

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[*] Judge Bryson assumed senior status on January 7, 2013.

[1] Allergan also asserted claims 1-3 of its U.S. Patent 6,403,649 ("the '649 patent"), and the district court likewise found the '649 patent was not invalid and infringed by Barr's and Sandoz's ANDAs. *Allergan*, 808 F.

Labs., Inc., 808 F. Supp. 2d 715, 717 (D. Del. 2011). Because the district court correctly construed the relevant claim term and determined the asserted claim was not obvious, we *affirm*.

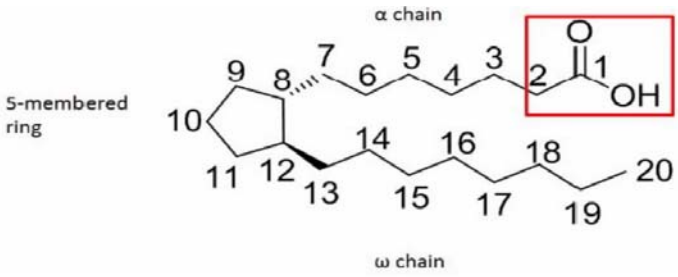
BACKGROUND

Allergan markets and sells Lumigan®, which was approved by the Food and Drug Administration ("FDA") to reduce intraocular pressure ("IOP") in people with ocular hypertension or glaucoma. The active ingredient in Lumigan® is bimatoprost. Allergan's '819 patent claims bimatoprost and methods of using bimatoprost to treat ocular hypertension or glaucoma.

1. Background of the Invention

In a healthy eye, proper IOP is maintained by aqueous humor, which is fluid between the cornea and the lens of the eye that transports nutrients like vitamins, sugars, and amino acids to the cornea. Too much aqueous humor disrupts IOP and poses a substantial risk factor for developing glaucoma. $PGF_{2\alpha}$ is a naturally-occurring prostaglandin that is known to lower IOP by increasing the outflow of aqueous humor from the eye. Prostaglandins are a class of naturally-occurring substances, all of which share the following twenty-carbon basic structure:

Supp. 2d at 736. However, the '649 patent expired on September 21, 2012 and thus is not at issue in this appeal.

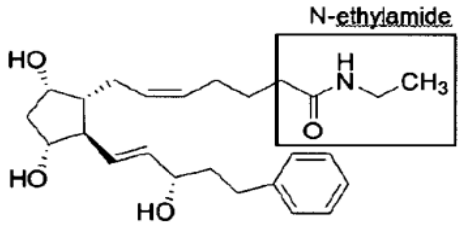


Allergan, 808 F. Supp. 2d at 719. The above carbon atoms are numbered from 1 to 20, with 1 through 7 forming an α (alpha) chain, 13 through 20 forming an ω (omega) chain, and 8 through 12 forming a five-membered (cyclopentane) ring. The C-1 position (highlighted by the box above) features carboxylic acid, which is present in all naturally-occurring prostaglandins.

As noted, it was known prior to the invention at issue that $PGF_{2\alpha}$ lowered IOP. The prior art also revealed that certain lipid-soluble esters of $PGF_{2\alpha}$ lowered IOP, and actually showed greater hypotensive effects than the parent compound $PGF_{2\alpha}$. '819 patent col. 2 ll. 9-38. According to the '819 patent's specification, however, prostaglandins like $PGF_{2\alpha}$ and its isopropyl ester were associated with negative side effects like "ocular surface hyperemia" (red eye) and "foreign-body sensation." *Id*. col. 2 ll. 41-46. The '819 patent discloses that certain compounds that replace the carboxylic acid group with a non-acidic substituent can reduce these side effects while retaining the desired IOP-lowering effect. *Id*. col. 3 ll. 9-18. One such compound is bimatoprost (cyclopentane N-ethyl heptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, $[1_{\alpha},2_{\beta},3_{\alpha},5_{\alpha}]$). *Id*. col. 7 ll. 44-46.

Bimatoprost is $PGF_{2\alpha}$, with an ethyl amide instead of a carboxylic acid group at the C-1 position and a phenyl

ring at C-17.[2] [J.A.10] Bimatoprost has the structure depicted below:

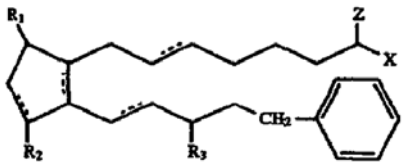


Allergan, 808 F. Supp. 2d at 720. Bimatoprost lowers IOP by increasing the flow of aqueous humor leaving the eye.

2. Patent-in-Suit

The '819 patent is related to and claims priority from U.S. Patent No. 5,352,708 ("the '708 patent"), filed on September 21, 1992. The '819 patent was issued on November 18, 1997, and was extended for 698 days as a result of the FDA's regulatory review of Lumigan®. Asserted claim 10 of the '819 patent ultimately depends from independent claim 5, which recites:

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



[2] Bimatoprost is a prostamide and is also known as 17-phenyl $PGF_{2\alpha}$ C-1 ethylamide.

> wherein . . . X is a radical selected from the group consisting of –OR^4 and –$N(R^4)_2$ wherein R^4 is selected from the group consisting o[f] hydrogen, a lower alkyl radical having from one to six carbon atoms,
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> 
>
> wherein R^5 is a lower alkyl radical having from one to six carbon atoms . . . .

'819 patent col. 13 l. 49 – col. 14 l. 7 (emphasis added to disputed claim term). Dependent claim 10 discloses five compounds that may be used in the treatment of ocular hypertension or glaucoma in which X is –$N(R^4)_2$. *Id.* col. 14 l. 55 – col. 15 l. 7. One of these compounds is bimatoprost, listed as cyclopentane N-ethyl heptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1_α,2_β,3_α,5_α]. Id. col. 15 ll. 1-3.

3. Barr's and Sandoz's Abbreviated New Drug Applications

On March 26, 2009, Barr filed an ANDA for a generic version of Lumigan®, listing Allergan's '819 patent as one of the Orange Book-listed patents associated with Lumigan®.[3] Barr's ANDA contained a Paragraph IV certification stating that Barr believed each relied-upon Orange Book patent was "invalid or [would] not be in-

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[3] The FDA lists all patents protecting FDA-approved drugs in a publication titled the "Approved Drug Products With Therapeutic Equivalence Evaluations," which is generally referred to as the "Orange Book." *Caraco Pharm. Labs., Ltd. v. Forest Labs., Ltd.,* 527 F.3d 1278, 1282 (Fed. Cir. 2008) (citing 21 U.S.C. § 355(b)(1), (c)(2)).

fringed by the manufacture, use, or sale of the new drug for which the application [was] submitted." 21 U.S.C. § 355(b)(2)(A)(iv). Sandoz likewise filed an ANDA for a generic version of Lumigan®, also with an accompanying Paragraph IV certification. Allergan filed patent infringement suits against Barr and Sandoz; the suits were consolidated into one action for a bench trial on patent invalidity and infringement.

4. District Court Proceedings

A. Claim Construction

The only claim term disputed before the district court was $–N(R^4)_2$ as used in claim 5, on which asserted claim 10 depends. The parties disagree whether or not $–N(R^4)_2$ requires identical R^4 substituents. If it does, bimatoprost's use of nonidentical R^4 substituents—hydrogen (H) and an ethyl group (CH_2CH_3)—would fall outside the protection of the '819 patent. The district court initially agreed with Barr and Sandoz that "the plain and ordinary meaning" of $–N(R^4)_2$ suggested that identical R^4 substituents were required; however, it ultimately found that Allergan had acted as its own lexicographer by defining $–N(R^4)_2$ to permit nonidentical R^4 elements. Therefore, the district court held that, as used in the '819 patent, the $–N(R^4)_2$ limitation did not require the R^4 substituents to be identical. *Allergan, Inc.*, 808 F. Supp. 2d at 726-27. Given this claim construction, the district court found that bimatoprost satisfied all limitations of the asserted claims, and consequently found Barr's and Sandoz's proposed uses of bimatoprost as set forth in their ANDAs constituted infringement of the '819 patent.

B. Invalidity

The district court found that asserted claim 10 of the '819 patent was not invalid, and rejected Barr and Sandoz's arguments based upon anticipation and obviousness. The primary invalidity reference asserted during trial was a patent to Johan Stjernschantz, published as Patent Cooperation Treaty Application No. WO 90/02253 on March 22, 1990 and entitled "Prostaglandin Derivatives for the Treatment of Glaucoma or Ocular Hypertension" ("Stjernschantz"). Barr and Sandoz's expert witness, Dr. Ashim Kumar Mitra, testified that asserted claim 10 was obvious over Stjernschantz, whether alone or in combination with other prior art, including unexamined Japanese Patent Application No. S49-69636 ("JP '636").[4] Barr and Sandoz also asserted post-trial that all of the asserted claims were obvious over Stjernschantz in combination with a chapter in the textbook "Prodrugs: Topical and Ocular Drug Delivery" entitled "Improved Ocular Drug Delivery with Prodrugs" ("Lee & Bundgaard").

Stjernschantz discloses IOP-reducing derivatives of certain prostaglandins. Two such derivatives are disclosed compounds 2 and 9, which are both isopropyl esters that convert into bimatoprost-free acid upon hydrolysis in the eye.[5] A third disclosed derivative is compound 17,

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[4] Other prior art discussed by Dr. Mitra at trial included: U.S. Patent No. 4,599,353, and a chapter of a 1977 textbook ("Design of Biopharmaceutical Properties through Prodrugs and Analogs") entitled "Physical Model Approach to the Design of Drugs with Improved Intestinal Absorption."

[5] Compound 9 differs from compound 2 only in that it has a single bond between C-13 and C-14, whereas compound 2 has a double bond in that position. Com-

bimatoprost-free acid or 17-phenyl $PGF_{2\alpha}$, which features a carboxylic acid functional group at C-1. The structural difference between bimatoprost and these Stjernschantz derivatives is that bimatoprost features an ethyl amide functional group at the C-1 position, whereas compounds 2 and 9 have an isopropyl ester at C-1, and compound 17 has carboxylic acid.

However, these obviousness theories were undermined when "Mitra's credibility was eviscerated on cross-examination." *Allergan*, 808 F. Supp. 2d at 733. Finding "Mitra's credibility flawed on a fundamental level," the district court accorded no weight to his testimony. *Id.* at 735. The court then declined to "review the prior art references and weigh their import absent the guidance of an expert." *Id.* at 736 n.21. Furthermore, based on its finding that Barr and Sandoz had improperly switched obviousness theories after Dr. Mitra's testimony was discredited, the district court held Barr and Sandoz had waived any obviousness theory that relied "primarily on JP '636, or that combine[d] Stjernschantz with Lee & Bundgaard." *Id.* at 735. Due to the lack of credible evidence to support Barr's and Sandoz's obviousness theories, plus the waiver of post-trial obviousness theories, the court held that Barr and Sandoz failed to prove obviousness of the asserted claim by clear and convincing evidence.

Barr and Sandoz filed this timely appeal. This court has jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

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pound 9 became latanoprost, which is marketed as Xalatan®, a leading antiglaucoma treatment.

DISCUSSION

1. The District Court Correctly Held That $-N(R^4)_2$ As Used in the '819 Patent Includes Compounds With Non-Identical R^4 Elements

The district court determined that "the plain and ordinary meaning of $-N(R^4)_2$ would support [Barr and Sandoz's] construction that the R^4 elements are identical functional groups," but went on to find that Allergan had acted as its own lexicographer in defining $-N(R^4)_2$ contrary to its ordinary meaning. *Allergan*, 808 F. Supp. 2d at 725-26. Barr and Sandoz appeal the district court's construction of the $-N(R^4)_2$ term, arguing that the plain and ordinary meaning of $-N(R^4)_2$ requires identical R^4 elements, and that Allergan failed to make any express statement departing from that plain and ordinary meaning.

Claim construction is a question of law subject to *de novo* review. *Cybor Corp. v. FAS Techs., Inc.,* 138 F.3d 1448, 1456 (Fed. Cir. 1998) (en banc). Claim terms are generally given their "ordinary and customary meaning" as they would be understood by a person of ordinary skill in the art. *Phillips v. AWH Corp.,* 415 F.3d 1303, 1312-13 (Fed. Cir. 2005) (en banc). "Importantly, the person of ordinary skill in the art is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the entire patent, including the specification." *Id.* at 1313. Indeed, "the context in which a term is used in the asserted claim can be highly instructive," as can other claims of the patent in question. *Id.* at 1314. The inventor's lexicography governs when "the specification [ ] reveal[s] a special definition given to a claim term by the patentee that differs from the meaning it would otherwise possess." *Id.* at 1316.

In this case, a person of ordinary skill in the art considering the entire '819 patent would construe the disputed $-N(R^4)_2$ term to encompass nonidentical R^4 elements. The disputed claim term arises in independent claim 5, in which $-N(R^4)_2$ is used to claim one of the molecules that may be located at the C-1 position of the compound. Claim 5 further recites that R^4 must be selected from a Markush group[6] "consisting of hydrogen, a lower alkyl radical having from one to six carbon atoms,

wherein R^5 is a lower alkyl radical having from one to six carbon atoms." '819 patent col. 13 ll. 31-39. [J.A.49] Asserted claim 10 ultimately depends from claim 5 and expressly includes three compounds with nonidentical R^4 elements, including bimatoprost.[7] Specifically, bimatoprost has two different substituents at the R^4 position, both of which are claimed in the Markush group: hydrogen (H) and an ethyl group (CH_2CH_3). *Id.* col. 14 l. 60 - col. 15 l. 7. Two other compounds listed in claim 10 also

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[6] "A Markush group is a listing of specified alternatives of a group in a patent claim, typically expressed in the form: a member selected from the group consisting of A, B, and C." *Abbott Labs. v. Baxter Pharm. Prods., Inc.*, 334 F.3d 1274, 1280 (Fed. Cir. 2003).

[7] Claim 9 ultimately depends from claim 5 and claims $-N(R^4)_2$ as one of the molecules at the C-1 position. '819 patent col. 14 ll. 56-57. Claim 10, in turn, depends from claim 9. *Id.* col. 14 l. 58. Therefore, although Barr and Sandoz stress that the $-N(R^4)_2$ term does not appear in claim 10, the compounds in claim 10 plainly contain $-N(R^4)_2$.

feature differing R^4 elements.[8] *Id*. col. 14 ll. 65-67; col. 15 ll. 4-6. Consistently, claim 18, depending from claim 11, recites the same three compounds as having a $–N(R^4)_2$ molecule at the C-1 position. *Id*. col. 17 ll. 14-22. These same three compounds, all with nonidentical R^4 substituents of $–N(R^4)_2$, also appear in the specification's list of "novel compounds [that] may be used in the pharmaceutical compositions and the methods of treatment of the present invention." *Id*. col. 7 ll. 19-21, 41-49.

Barr and Sandoz nevertheless focus on the district court's preliminary conclusion that the plain and ordinary meaning of $–N(R^4)_2$ required identical R^4 elements. However, this preliminary conclusion was based on extrinsic evidence, such as expert testimony that "[t]he $(X)_y$ nomenclature" was "commonly used" to represent identical substituents, *Allergan,* 808 F. Supp. 2d at 725, which failed to consider the $–N(R^4)_2$ term as it was used in the '819 patent. *Phillips*, 415 F.3d at 1321 ("Properly viewed, the 'ordinary meaning' of a claim term is its meaning to the ordinary artisan *after reading the entire patent*.") (emphasis added). When the district court later considered the term in the context of the '819 patent, it concluded that Allergan "clearly manifest[ed]" in the claims and specification that the $–N(R^4)_2$ term was meant to encompass nonidentical R^4 elements such as bimatoprost. *Allergan*, 808 F. Supp. 2d at 726. Barr and Sandoz's argument regarding the plain meaning of $–N(R^4)_2$ is unpersuasive; when properly construed in light of the

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[8] These compounds are: cyclopentane N-*isopropyl* heptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, $[1_\alpha,2_\beta,3_\alpha,5_\alpha]$, and cyclopentane N-*methyl* heptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, $[1_\alpha,2_\beta,3_\alpha,5_\alpha]$. '819 patent col. 14 ll. 65-67; col. 15 ll. 4-6 (emphases added).

entire patent, the $-N(R^4)_2$ term plainly encompasses nonidentical R^4 substituents.

2. The District Court Correctly Held That the Asserted Claim Is Not Invalid As Obvious

The district court held that Barr and Sandoz failed to prove obviousness by clear and convincing evidence. Barr and Sandoz appeal this determination. First, they argue that the district court's adverse credibility determination of Dr. Mitra did not excuse the court from its obligation to independently review the submitted prior art references. Additionally, they assert that their obviousness theories are supported even when considering only the testimony of Allergan's experts and corroborating evidence.

"The ultimate judgment of obviousness is a legal determination," *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 427 (2007), which we review *de novo*, *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 993 (Fed. Cir. 2009). Following a bench trial, underlying findings of fact are reviewed for clear error. *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1289 (Fed. Cir. 2006). A party seeking to invalidate a patent based on obviousness must prove such obviousness by clear and convincing evidence. *Procter & Gamble Co.*, 566 F.3d at 993-94. A patented invention is obvious when "a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and [ ] the skilled artisan would have had a reasonable expectation in doing so." *Pfizer, Inc. v. Apotex, Inc.,* 480 F.3d 1348, 1361 (Fed. Cir. 2007).

A. The District Court Did Not Err In Finding Expert Testimony Was Required To Show Invalidity

The district court found that Dr. Mitra's credibility was "flawed on a fundamental level" and declined to assign any weight to his opinions. *Allergan*, 808 F. Supp. 2d at 735. This was a fair assessment of the testimony of Dr. Mitra, whose prevarication and inconsistency were repeatedly demonstrated during Allergan's cross examination. For instance: (1) Dr. Mitra incorrectly drew the bimatoprost molecule and utilized slides that inaccurately represented bimatoprost; (2) his previous testimony given at another trial directly contradicted his stated opinion that Stjernschantz persuasively showed the hypotensive effect of prostaglandin analogues; and (3) his previously published opinions that bimatoprost was more effective than latanoprost and acted through a "novel prostamide receptor" contradicted his trial testimony that bimatoprost was just a "delivery vehicle" for bimatoprost-free acid. *Id*. at 733-34.

The district court declined to independently "review the prior art references and weigh their import absent the guidance of an expert." *Allergan*, 808 F. Supp. 2d at 736 n.21. On appeal, Barr and Sandoz challenge this refusal to consider their obviousness theories, contending that discrediting Dr. Mitra "did not then permit the [district] court to ignore all other evidence. . . ." BB.49.

This court has noted that "'expert testimony regarding matters beyond the comprehension of laypersons is sometimes essential,' particularly in cases involving complex technology." *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1240 n.5 (Fed. Cir. 2010) (quoting *Centricut, LLC v. Esab Group, Inc.*, 390 F.3d 1361, 1369-70 (Fed. Cir. 2004)). Obviousness is one area in which expert testimony may be required. *See Proveris Scientific Corp. v. Innovasystems, Inc.*, 536 F.3d 1256, 1267 (Fed. Cir. 2008)

(holding the district court did not abuse its discretion "in requiring [the party asserting invalidity] to present expert testimony in order to establish invalidity" because the technology was "sufficiently complex to fall beyond the grasp of an ordinary layperson."). In complex cases where invalidity on the grounds of obviousness is asserted, "expert testimony may be critical, for example, to establish the existence of certain features in the prior art or the existence (or lack thereof) of a motivation to combine references." *Wyers*, 616 F.3d at 1240 n.5 (interior references omitted).

The district court appears to have found this case to be "sufficiently complex to fall beyond [the] grasp of ordinary layperson[s]." *Allergan*, 808 F. Supp. 2d at 736 n.21 (characterizing the holding of *Proveris Scientific Corp.*, 536 F.3d at 1367). Indeed, this is not a case where "[t]he technology is simple," *Sundance, Inc. v. DeMonte Fabricating Ltd.*, 550 F.3d 1356, 1365 (Fed. Cir. 2008), or where the references are "easily understandable without the need for expert explanatory testimony," *Union Carbide v. American Can Co.*, 724 F.2d 1567, 1573 (Fed. Cir. 1984). Additionally, this is emphatically not a case where "[t]he factual inquiries underlying [the] determination of obviousness are not in material dispute." *Sundance, Inc.*, 550 F.3d at 1365; *see*, *e.g., Allergan, Inc.,* 808 F. Supp. 2d at 721 (explaining that "[b]imatoprost's mechanism of action is greatly debated in this case," with Barr and Sandoz arguing it functions as a "prodrug" with no inherent biological activity, and Allergan arguing that it is not a prodrug, but rather acts on a novel prostamide receptor). Although in some cases, "the legal determination of obviousness may include recourse to logic, judgment, and common sense, in lieu of expert testimony," *Wyers*, 616 F.3d at 1239, the district court did not err in finding that common sense and logic were not sufficiently illuminating

in this case to carry Barr and Sandoz's burden of proving obviousness.

B. Allergan's Expert's Testimony Does Not Support Barr and Sandoz's Obviousness Theories

On appeal, Barr and Sandoz argue that their obviousness theories are supported by expert testimony: that of Allergan's expert, Dr. Timothy L. Macdonald, whose testimony the district court found to be credible.[9] In particular, they contend that Dr. Macdonald's testimony supports the three facts needed to show the asserted claim is obvious in view of Stjernschantz and other references: (1) Stjernschantz taught that bimatoprost-free acid lowered IOP; (2) Stjernschantz's compound 2 hydrolyzed into bimatoprost-free acid when placed in the eye; and (3) a skilled artisan would have known that substituting an amide for the ester at the C-1 position would result in a prodrug that hydrolyzed into bimatoprost-free acid in the eye.

Dr. Macdonald provided testimony consistent with the first two propositions. *See* J.A.2086 (testifying that Stjernschantz taught bimatoprost-free acid would have the effect of lowering IOP); J.A.2062-63 (testifying that Stjernschantz taught compound 2 would hydrolyze into bimatoprost-free acid once in the body). However, his testimony contradicts the third requirement. Dr. Macdonald instead asserted that one of skill in the art would not have believed substituting an amide at the C-1 position would create a prodrug that hydrolyzed into bimato-

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[9] Barr and Sandoz also rely on other Allergan witnesses to support their obviousness claim, but we have carefully reviewed the record and find nothing in the testimony of these additional witnesses that could override Dr. Macdonald's expert opinion of non-obviousness or establish clear and convincing evidence of obviousness.

prost-free acid once in the eye. To the contrary, Dr. Macdonald testified that an amide converts into carboxylic acid at such a slow rate that "one doesn't consider it as a candidate [as a prodrug]." J.A.2065-66. He explained that "a prodrug approach relies on efficient conversion of the prodrug into the drug," and the "500-year half life" of an amide in water was "not an efficient conversion." J.A.2067; *see also* J.A.1996. Dr. Macdonald concluded that the prior art did not teach or motivate one of skill in the art to substitute an amide at the C-1 position to create a glaucoma drug. Given Dr. Macdonald's testimony to the contrary, Barr and Sandoz can point to no credible expert testimony showing that substituting an amide at the C-1 position would have been obvious to a skilled artisan at the time of the invention. Because of this gap, we hold that Barr and Sandoz have failed to show obviousness of the '819 patent by clear and convincing evidence.[10]

CONCLUSION

For the foregoing reasons, we affirm the district court's claim construction and determination of nonobviousness.

AFFIRMED

[10] We need not determine whether the district court abused its discretion in finding that Barr and Sandoz waived their post-trial obviousness theories, because, as determined above, the record contains insufficient expert testimony to support any of Barr and Sandoz's obviousness theories.