20-1723

United States Court of Appeals for the Federal Circuit

AMARIN PHARMA, INC. and AMARIN PHARMACEUTICALS IRELAND LIMITED,

Plaintiffs/Appellants,

v.

HIKMA PHARMACEUTICALS USA INC., HIKMA PHARMACEUTICALS INTERNATIONAL LIMITED, DR. REDDY'S LABORATORIES, INC. and DR. REDDY'S LABORATORIES, LTD.,

Defendants/Appellees,

APPEAL FROM THE U.S. DISTRICT COURT FOR THE DISTRICT OF NEVADA, IN CASE NO. 2:16-CV-02525-MMD, JUDGE MIRANDA M. DU

APPELLANTS' REPLY BRIEF

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June 26, 2020

CERTIFICATE OF INTEREST

Counsel for the Appellant, Amarin Pharma, Inc., and Amarin Pharmaceuticals Ireland Limited, certifies the following:

1. The full name of every party represented by me is: Amarin Pharma, Inc., and Amarin Pharmaceuticals Ireland Limited

2. The name of the real party in interest (please only include any real party in interest NOT identified in Question 3) represented by me is: Amarin Corporation plc

3. Parent corporations and publicly held companies that own 10% or more of stock in the party: Both Amarin Pharma, Inc. and Amarin Pharmaceuticals Ireland Limited are wholly-owned subsidiaries of Amarin Corporation plc

4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court (**and who have not or will not enter an appearance in this case**) are:

McDonald Carano LLP: Adam Hosmer-Henner; Chelsea Latino
Covington & Burling LLP: Einar Stole; Michael N. Kennedy; Megan P. Keane; Alaina M. Whitt; Han Park; Jordan L. Moran; Daniel J. Farnoly
Santoro Whitmire, Ltd.: Nicholas J. Santoro; Jason D. Smith

5. The title and number of any case known to counsel to be pending in this or any other court or agency that will affect or be directly affected by this court's decision in the pending appeal. *See* Fed. Cir. R. 47.4(a)(5) and 47.5(b): *Amarin Pharma, Inc. v. Dr. Reddy's Labs., Inc.*, 2:18-cv-01596-MMD-NJK (D. Nev.), on appeal as No. 20-1901 (Fed. Cir.)

Dated: June 26, 2020

/s/ *Jonathan E. Singer*

cc: counsel of record

TABLE OF CONTENTS

Page

TABLE OF CONTENTS (cont'd)

Page

TABLE OF AUTHORITIES

Page(s)

Cases

TABLE OF AUTHORITIES (cont'd)

Statutes

INTRODUCTION

Long on pejoratives, Defendants' brief seeks to accuse its way to affirmance of the district court's erroneous obviousness judgment. But no amount of rhetoric can cure the myriad defects with that judgment.

On the objective indicia, the district court found "clear and convincing evidence" of obviousness "as an initial matter" (Appx57) before addressing the legal impact of those indicia. This was error that had real consequences. Because it had already found Amarin's invention obvious, the district court shaped the objective indicia evidence to fit its premature and flawed conclusion, nakedly devaluing the long-felt need and commercial success proven by Amarin; finding a lack of skepticism, praise, and unexpected results on grounds Defendants cannot support; and even pitting the objective indicia Amarin proved against those Amarin allegedly had not.

The district court's errors in the prima facie case were equally case-turning. At the key juncture, the district court merely copied verbatim Defendants' proposed finding that there was "no reason" for the skilled artisan to expect that LDL-C levels of severe hypertriglyceridemia patients responded differently to treatment than those with milder forms of the disease. (Appx60.) But this required the district court to ignore prior experience with niacin, fibrates, Lovaza®, and even diet, which showed the exact difference the district court found lacking. The skilled artisan does not behave in this fashion—rather, she considers the entire prior art for what it teaches.

And here, the prior art taught that, at the time of the invention, severe hypertriglyceridemia patients—including those at "exactly" 500 mg/dL—had "jammed up" triglyceride-clearing systems that produced large LDL-C increases when any treatment that "un-jammed" them. (Appx1395–1396.) Dr. Manku's invention, which avoids those increases, was not obvious in the face of this prior art. The district court's judgment should be reversed.

ARGUMENT

I. Hindsight Bias Clouded the District Court's Consideration of Powerful Objective Indicia Evidence

A. The District Court's Premature Conclusion of Obviousness, Before Considering the Objective Indicia, Was Not Harmless Error

As Amarin explained in its opening brief, the district court got the wrong answer because it asked the wrong question. Instead of determining whether Amarin's claims were obvious after considering all of the evidence, including the objective indicia, the district court pre-judged obviousness based on a "prima facie" case and then turned to the objective indicia only to see if Amarin could change the court's mind. This was legal error. *See, e.g.*, *In re Cyclobenzaprine,* 676 F.3d 1063, 1077 (Fed. Cir. 2012); *Lindemann Maschinenfabrik GMBH v. Am. Hoist & Derrick Co.*, 730 F.2d 1452, 1461 (Fed. Cir. 1984).

In their brief, Defendants pretend (*e.g.* at 28) that Amarin's complaint is only about the language the district court used in reaching its determination, arguing that the district court's use of terms such as "overcome" and "prima facie" do not amount

to error. Or that Amarin merely objects to where in the opinion the district court discussed the objective indicia—asserting (*e.g.* at 30) that the district court could not have decided obviousness based on the prima facie case alone because, before discussing that case, the district court made factual findings about some objective indicia.

But Amarin's complaint is about substance. Amarin's opening brief (*e.g.* at 44–45) recognized that a court may correctly analyze obviousness utilizing a framework that looks to a "prima facie" case and then to objective indicia—provided that the court withholds its conclusion until considering the objective indicia. And while amici suggest that this Court should consider prohibiting use of this framework—a change Amarin would welcome to prevent errors like those committed here—this Court need not overturn precedent to resolve this case. The district court's error was not limited to its choice of words or structure, but rather that, substantively, it found obviousness based on the prima facie case alone and then required Amarin to "save" the claims through the objective indicia. (Appx56.)

On this substance, Defendants' brief is largely silent in the district court's defense. Defendants fail to defend the district court's explicit statement, in the very first line of the district court's analysis of the prima facie case, that "[a]s an initial matter, the Court is persuaded that Defendants presented clear and convincing evidence at Trial that all Asserted Claims are invalid as obvious." (Appx57.) Defendants' main response (at 28, 30) is to say that the district court couldn't have

meant what it said—either because the district court later said it considered the objective indicia or because, according to Defendants, what the court meant concerned burdens of production, not persuasion. But Defendants cannot simply ignore the substance of what the district court said. The district court didn't say that it found that Defendants had presented a strong prima facie case—rather, in the prima facie case, it began by concluding the claims were obvious "by clear and convincing evidence." (Appx57.) It immediately followed that up by concluding that the use of EPA in place of the EPA and DHA of Lovaza® was "an obvious substitution, obtained by combining the Lovaza PDR and Mori" without any hint that the objective indicia played any role in these conclusions. (*Id.*)

That these premature conclusions then infected the district court's actual analysis of the objective indicia is plain. In considering Amarin's demonstration of satisfaction of long-felt need, for example, the district court explicitly devalued that demonstration because the court believed the solution to be prima facie obvious: "[t]hus the Asserted Claims represent an improvement—albeit a prima facie obvious one—over the prior art. And this secondary consideration ***therefore*** weighs slightly in favor of finding the Asserted Claims nonobvious. (Appx67 (emphasis added).)

Statements like these are remarkable, and make this case fundamentally different from *Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 719 F.3d 1346, 1352 (Fed. Cir. 2013), on which Defendants heavily rely. In *Novo*, this Court recognized that a district court commits legal error by reaching a determination of obviousness

before considering objective indicia evidence. *See id.* at 1353. The problem in the case wasn't the legal theory, but rather that "[n]othing in the court's opinion in th[at] case indicate[d] that [the court] reached a premature conclusion on obviousness" before considering the objective indicia. *Id.* at 1354.

Here, by contrast, we know the district court reached a "premature conclusion on obviousness" because it explicitly said so. (Appx57.) The court then devalued the objective indicia and the evidence supporting them based on that already-reached conclusion. Defendants are thus wrong (at 31-33) to write off any error in the district court's weighing of the objective indicia as harmless. That evidence all pointed strongly to non-obviousness because it fundamentally contradicted the prima facie case. For example, if EPA as a treatment for severe hypertriglyceridemia without raising LDL-C was obvious from the prior art on Epadel®, why didn't Mochida bring it to the United States and reap the profits from its long-standing product? And if Mori was such strong evidence of obviousness, why did experts who were aware of it nonetheless believe LDL-C would rise when Amarin tested EPA? Defendants' assertion that the failure to accord this evidence proper weight is "not, by itself, reversible error" (at 32), is belied by these types of questions, and finds no support in this Court's authorities. *See, e.g.*, *Lindemann*, 730 F.2d at 1461.

The district court's premature conclusion also appears to have caused its impermissible and inexplicable weighing of the objective indicia ***against each other***.

(Appx69.) Defendants appear to concede that such a weighing is impermissible, but argue that the district court didn't really mean what it said.

Defendants are wrong (at 30) to write off this error as a "single sentence" in the district court's opinion. The statement appeared in the section of the court's opinion summarizing its determinations regarding the objective indicia. (Appx69.) That section contains, in total, just six sentences—so a legal error in even a single sentence is a serious matter.

Defendants are also wrong that the context of the sentence in any way changes its meaning. For one, the district court should be taken to mean what it said, which was that objective evidence favoring non-obviousness was "outweighed by the fact that the Court found Plaintiffs' other proffered secondary considerations favor defendants"—explicitly weighing the two categories against each other. (*Id.*) For another, the context of the sentence only makes this error more grievous. The weighing of objective indicia against each other was the only reason the district court gave for its conclusion that Amarin's objective indicia evidence, as a whole, was "weak." (*Id.*) Thus, the context shows that the district court predicated its consideration of the objective indicia on its flawed legal premise, which was part and parcel of its impermissible burden-shifting approach on obviousness as a whole.

B. Defendants' Attempts to Justify the District Court's Dismissal of Objective Indicia Evidence on Grounds Not Articulated by the District Court Should Be Rejected

Tellingly, despite an outward posture that the district court's legal reasoning contains no error, Defendants attempt to justify the district court's conclusions regarding objective indicia on numerous new grounds, and liberally assign factual error where the district court found against Defendants. The Court should reject these arguments.

Commercial Success. To prove nexus, Amarin needed to show the commercial product enjoying success was co-extensive with the claimed invention. *See, e.g.*, *Polaris Indus., Inc. v. Arctic Cat, Inc.,* 882 F.3d 1056, 1072 (Fed. Cir. 2018). Amarin did so. In its opinion, the district court concluded that VASCEPA® "embodies the Asserted Claims" (Appx39)—a finding Defendants do not challenge.

Even if only patented sales matter, Amarin's expert testified that VASCEPA® is a commercial success—enjoying a "six-fold increase in sales over time." (*See* Appx2189:11–16; *see also* Appx246 ¶¶ 829–830; Appx2183–2184.) Doing the math, VASCEPA®'s patented sales, even if only 25% of the market by 2018, still amounted to over $50 million annually, and have totaled over $200 million since launch. (*See* Appx2189:17–24; *see also* Appx1976:20–24; Appx2195:4–7.)

The district court credited Amarin's analysis of commercial success as "robust and reliable" and consistent with Defendant Hikma's internal analysis. (*See* Appx42;

see also Appx39–42; Appx69.) Defendants show no error in the district court's conclusion.

Long-Felt But Unmet Need. Defendants also ask this Court to revisit the district court's findings concerning long-felt but unmet need. Defendants contend (at 36-39) there was no long-felt need, but only a delay to develop a drug like VASCEPA® because of a purported lack of commercial incentive. Defendants are wrong.

As to the size of the relevant patient populations, while the number of severe hypertriglyceridemia patients is certainly much less than those with less elevated triglycerides, three million patients who must be treated chronically is hardly a "niche" market. (Red. Br. at 38.) By comparison, "orphan drugs" are capped at 200,000 patients. 21 U.S.C.A. § 360bb(a)(2).

Defendants' argument also fails to account for Lovaza®'s introduction to the U.S. market in 2004. The makers of Lovaza® apparently had enough commercial incentive to pursue and obtain FDA approval then, and this incentive surely existed in 2000, the date of the Mori and Kurabayashi references; and in 1995, the date of the Hayashi paper. This Court should believe the market, which shows that companies had the incentive to develop treatments for severe hypertriglyceridemia, yet failed to fill the need for a treatment that did not raise LDL-C until Amarin developed VASCEPA®.

Defendants' contention that the JELIS study suggested that pure EPA might also be beneficial for a different condition—prevention of major coronary events in patients with merely elevated triglycerides—is immaterial, as that says nothing about a motivation to pursue a treatment for severe hyperglyceridemia, commercial or otherwise. (*See, e.g.*, Appx1768:7–9 (Defendants' expert, admitting that the "baseline triglyceride levels in JELIS" were "just above the normal range"); *see also* Appx2499:12–18*;* Appx103230 ¶ 622.)

Defendants are also wrong to downplay (at 37) the importance of having a single drug to treat severe hypertriglyceridemia, repeating their rejected arguments that adding a statin to Lovaza® was sufficient. But doctors strongly prefer using a single drug, as opposed to multiple drugs, because patients often stop taking the co-prescribed drug. (Appx1412–13 (Heinecke).) Defendants' answer is also of no comfort to those patients who couldn't tolerate statins or who needed them to lower their pre-existing LDL-C levels yet received no benefit from the statins other than to offset the LDL-C increases caused by their treatments for severe hypertriglyceridemia. (Appx2352–2353 (Toth).)

Lastly, Defendants are wrong to dismiss (at 39) the choice made by the developers of Lovaza® to use EPA ***and*** DHA, despite Mori purportedly teaching they should have used EPA alone. Regardless of when development of Lovaza® began, Mori predated Lovaza® by years. If, as Defendants contend, Mori showed that EPA alone was the solution, and that DHA was the cause of the problems with

Lovaza®, it defies logic that the developers of Lovaza® would ignore this and continue with a plan they knew would result in a sub-standard treatment, leaving the EPA opportunity for a competitor. Dr. Manku's invention fulfilled a long-felt, but unmet need.

Skepticism. Below, the district court dismissed Amarin's evidence of skepticism because it mistakenly thought the experts Amarin tasked with evaluating its proposed clinical trials were unaware of Mori, and because the court disagreed with the skepticism based on its post-hoc reading of Mori. (Appx68.) This was both clear factual error—contemporaneous documents show the experts ***were*** aware of Mori (*see, e.g.*, Blue Br. at 39-40)—and legal error resulting from the district court's prejudgment of obviousness. Defendants do not even attempt to defend the district court's reasoning.

Defendants' argument that Amarin waived consideration of the expert panel's skepticism because Amarin only asserted skepticism as to the cardiovascular benefits of VASCEPA® is belied by the fact that the district court specifically addressed, albeit erroneously, skepticism as to whether EPA would raise LDL-C, based on the very document in dispute, which Amarin highlighted in its post-trial briefing. (*See* Appx68; Appx103295.) Defendants ignore this, while also ignoring Dr. Manku's testimony, which detailed his uphill battle in convincing others of his insights. (*See* Appx4193 at 82:9–18). In this regard, Defendants' portrayal of the expert panel's 2008 skepticism as a "lack of enthusiasm" (at 36) falls flat. This was not mere ambivalence—this was

disbelief by experts hired to evaluate Amarin's clinical plans on the precise point of alleged obviousness. When this evidence receives its proper due, skepticism weighs heavily in favor of non-obviousness.

Praise. The evidence relating to praise should also be re-weighed. The district court rejected the praise because Amarin's results were so unbelievable that the experts offering praise were skeptical of the results, while at the same time recognizing that "if you can have favorable cardiovascular effects without raising LDL cholesterol, that's going to be an advantage." (Appx88649.) Moreover, regardless of whether a single doctor out of many quoted in the article believed that available treatments for severely hypertriglyceridemia were good enough, the overall reaction to Amarin's invention from the article was overwhelmingly positive and weighs in favor of non-obviousness.

Unexpected Results. As in our opening brief, we primarily discuss these in relation to the district court's asserted prima facie case. However, Defendants' attempt to reframe the district court's clear error in ruling that the PTO had not considered Kurabayashi contradicts the law. *See Shire LLC v. Amneal Pharms., LLC*, 802 F.3d 1301, 1307 (Fed. Cir. 2015) (examiners are presumed to "have considered" references "listed on the face of" patents). The district court did not say that the examiner did not discuss Kurabayashi in any office action, as Defendants (at 53) assert. Rather, the district court said the examiner "did not consider" Kurabayashi, citing caselaw that the PTO "'did not have all material facts before it.'" (Appx66.)

This is clear error, and further highlights the district court's legal error. Like its erroneous assumption that Amarin's expert panel could not have been aware of Mori because the district court disagreed with those experts, the district court ruled precipitously that the examiner was unaware of Kurabayashi because the district court had already ruled that Kurabayashi rendered Amarin's invention obvious. The district court's erroneous shaping of the objective indicia evidence because of its premature obviousness conclusion is clear and warrants reversal.

II. Defendants Cannot Excuse the District Court's Errors in Finding Motivation and Reasonable Expectation of Success

A. The District Court's Extrapolation of the Effects of EPA in Patients with Mild to Moderately Elevated Triglycerides to Patients with Severe Hypertriglyceridemia Was Error

Just as the district court did, Defendants continue to brush aside the critical issue of the patient population required by every claim—patients with severe hypertriglyceridemia, i.e., triglyceride levels of ≥500 mg/dL, a threshold defined by medical guidelines. (Appx49988.) None of Mori, Hayashi, or Kurabayashi concern studies for the treatment of severe hypertriglyceridemia. This is not a disputed matter. (Appx1492–1497.)

The question for this Court then is whether there was clear and convincing evidence to support extrapolating data from the one population—the mild to moderate hypertriglyceridemic population of Mori, Hayashi, and Kurabayashi—to the severe hypertriglyceridemic population of the asserted claims. Plainly, there is not.

The only evidence at trial from the time of the invention on the behavior of triglyceride-reducing drugs in severe hypertriglyceridemia[1] is that the drugs caused large increases in LDL-C. Whether it was niacin, fibrates or Lovaza®/Omacor®, "dramatic[] increase[s]" in LDL-C on the order of 40-50% were the norm. (Appx5; Appx1450–1451 (Heinecke); Appx2328–2345 (Toth); Appx887 (Budoff); Appx110064; Appx49778–49787; Appx43935–43942; Appx88408–88411; Appx44323–44324; Appx48910–48911.) But these same drugs did ***not*** cause such LDL-C increases in the less elevated triglyceride (150 up to 499 mg/dL) populations. (*Id.*) Thus, the prior art taught that, with respect to LDL-C, patients with severe hypertriglyceridemia responded differently to triglyceride-lowering drugs than patients with less elevated triglycerides.[2]

[1] Defendants raise other art with a patient or two with baseline triglyceride levels greater than 500 mg/dL in an attempt to contradict Amarin's showing that the prior art had not thought to treat the severe hypertriglyceridemia population with EPA. (Red. Br. at 11–12.) Obviously, a patient or two is not a population, and none of this art discussed any of these individuals' LDL-C levels. In this same vein, Defendants' claims about Dr. Lavin's confessed error in his prosecution declaration are wildly overstated. The examiner's allowance did not rely on that declaration but rather on amended claim language the examiner proposed that gave patentable weight to the Apo-B and LDL-C limitations. (Appx87862–70; Appx87901; Appx88046–53.)

[2] Defendants (at 49-50) brazenly offer the 2007 Lipitor® label as allegedly evidencing a treatment that reduced triglycerides without raising LDL-C in severe hypertriglyceridemia. This is pure gamesmanship. Defendants did not include the Lipitor® label as a prior art reference on their 35 U.S.C. § 282 statement, or in their

The understood reasons for this phenomenon are clear. As Defendants' expert aptly put it, "we knew [in 2008] that somewhere above 500 milligrams per deciliter the system for clearing triglycerides jams up." (Appx1395–1396.) While perhaps this mechanistic difference isn't "magical," whatever that might mean, it is nonetheless crucial. This jammed up system has a genetic origin, as the district court agreed (Appx48), and, at the time of the invention, triglyceride-lowering treatments were believed to break the "logjam" in these genetically-disfavored patients by activating enzymes to convert large volumes of excess VLDL particles to LDL particles, producing the dramatic increases in LDL-C. (Appx2344–2351; Appx2315–2318 (Toth); Appx48848.)

Defendants, and the district court, never explained why they thought this understanding was incorrect, or why it would not have led skilled artisans to conclude that a drug for lowering triglycerides in severe hypertriglyceridemia would likely raise LDL-C substantially, regardless of its effect in other populations. Even now, Defendants' brief does not so much as mention the word "mechanism," even though it is critical for setting the expectation of a skilled artisan.

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expert reports, depriving Amarin of the opportunity to present evidence about what that label means. This is improper. *Ferguson Beauregard/Logic Controls, Inc. v. Mega Sys., LLC*, 350 F.3d 1327, 1347 (Fed. Cir. 2003). In any event, FDA did not approve Lipitor® to treat severe hypertriglyceridemia, and it would not have been an appropriate treatment for the condition. (Appx2602; Appx2765; Appx2771; Appx49992; *see also* Appx2611–2612 (Lipitor® data does not permit conclusions about severely hypertriglyceridemic patients).)

Defendants instead continue to insist (at 47) that the evidence of dramatic LDL-C increases seen with Lovaza®, fibrates, niacin and even diet is "irrelevant." While this strategy was successful at the district court, this Court should decline the invitation to rule that the only relevant evidence concerns the effects of pure EPA in different patient populations. The obviousness analysis requires examination of all the prior art, and, if art is to be discounted, there must be a valid reason for doing so. *See, e.g.*, *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1550 (Fed. Cir. 1983); *Institut Pasteur v. Focarino*, 738 F.3d 1337, 1344–46 (Fed. Cir. 2013).

The district court's unexplained failure to consider this art as a whole was thus error. But even if the district court found sub silencio that skilled artisans would not have considered the other products, as Defendants imply, this was erroneous. Contemporaneous prior art showed that skilled artisans viewed the LDL-C increase as a general phenomenon, based on the understood consequence of undoing the logjam in triglyceride clearance, and thus discussed the different products together. The 2008 Bays article on Lovaza® explained that "***[a]s with fibrates***, the degree of LDL-C elevations observed with [omega-3] treatment is ***generally related to the pretreatment TG levels***" and that "[t]he reason for the increased LDL-C levels with [omega-3 fatty acids] is related to the increased conversion of VLDL particles to LDL particles." (Appx44256–44258 (emphases added); Appx2350–2351 (Toth).) In 2007, McKenney also compared Lovaza® with "***fibric acid derivatives (fibrates) and nicotinic acid (niacin***)," and explained that, for all these treatments, "***[a]n increase***

in low-density-lipoprotein (LDL) and high-density-lipoprotein (HDL) cholesterol can accompany a reduction in triglycerides; ***the higher the baseline triglyceride level, the greater these lipids may be increased***." (Appx48848 (emphases added); *see also* Appx2345–2349 (Toth).)

Defendants have no comment on these articles for this Court even to consider, and thus do not explain why, when skilled artisans thought it was proper to compare the LDL-C effects of fibrates and niacin with Lovaza®, an omega-3 containing product, they would not also have compared these products with the omega-3 EPA. Indeed, the experts that Amarin consulted with on its clinical plans ***in fact*** made such a comparison, stating that, with pure EPA, "LDL-C is likely to go up ***as it does with virtually all tg lowering therapies in this group of patients***." (Appx47720 (emphasis added).)[3]

In the face of this evidence, the district court's unreasoned extrapolation of data from the non-severe elevated triglyceride populations to severe hypertriglyceridemia was error. Defendants' citation (at 41) of *Persion Pharmaceuticals*

[3] Defendants simply dodge the import of the notes from the expert panel meeting in their brief. Instead, Defendants (at 16) feature an e-mail from Dr. Bays to argue that the LDL-C results were not unexpected, contrary to his published article that says they were. Dr. Bays testified that he was unsure what he meant in that e-mail, which pre-dated the peer-reviewed article, because his "expectation was, prior to getting the results of the MARINE trial, … that the LDL cholesterol levels would rise after administration of AMR101 in patients with very high triglyceride levels." (Appx3437–3439; Appx3445–3447; *see also* Appx48679.)

LLC v. Alvogen Malta Operations, Ltd., 945 F.3d 1184 (Fed. Cir. 2019) only serves to confirm this. In that case, the claims covered patients with hepatic impairment, while the asserted prior art discussed healthy patients. However, the prior art also taught that healthy patients and hepatically impaired patients had "similar" pharmacokinetic results. *Persion*, 945 F.3d at 1193. The district court thus properly extrapolated from the healthy population to the hepatically impaired population for this "similar" property. *Id.* Here, by contrast, the prior art counsels that treatment of severe hypertriglyceridemia resulted in LDL-C levels that were anything but "similar" to those in milder hypertriglyceridemia. Without anything to connect the two, the district court's extrapolation was error. *See OSI Pharms., LLC v. Apotex Inc.*, 939 F.3d 1375, 1385 (Fed. Cir. 2019) (reversing obviousness because, in part, the prior art disclosed no "reliable indicator of success").

B. Defendants' Attempts to Fill the Gap in the District Court's Reasoning Fail

In the face of this prior art, Defendants (at 44-45) retreat to Dr. Heinecke's credited, conclusory opinion that a skilled artisan would reasonably expect from Mori et al. that EPA would not raise LDL-C in the severe hypertriglyceridemia population. But Dr. Heinecke extended those studies to severe hypertriglyceridemia merely by agreeing with counsel that, in his opinion, a skilled artisan would not "have expected a different result in patients above 500," and not, for example, by citing to prior art that supported such an expectation. (Appx1399.) The district court's analysis was equally

conclusory—relying on off-point testimony from Dr. Toth that medications that reduced ***triglycerides*** in patients with triglycerides below 500 would likely also reduce ***triglycerides*** in patients with severe hypertriglyceridemia and then faulting Amarin for providing "no reason to expect differently for LDL-C" in the key finding copied from Defendants. (Appx60.)

This Court's authorities require more. A conclusory expert opinion that contradicts the prior art is not clear and convincing evidence of obviousness. *See TQ Delta, LLC v. CISCO Sys., Inc.*, 942 F.3d 1352, 1358–61 (Fed. Cir. 2019).

Tacitly recognizing this, Defendants try to bridge the gap in multiple, deficient ways. First, Defendants argue (at 45-46) that the prior art need not have the required evidence because Amarin's patents don't prove with clinical data that LDL-C will not increase with EPA in severe hypertriglyceridemia. But this really relates to Defendants' waived written description defense, and is the same type of argument this Court rejected in *Cyclobenzaprine*. There, challengers argued that the lack of PK/PD relationship data in the prior art could be excused because the patent-in-suit lacked therapeutic efficacy data, but this Court explained that "[l]ack of written description … is a separate defense" and not part of the obviousness analysis. 676 F.3d at 1070.

Defendants' reliance on *Merck & Co. v. Teva Pharmaceutical USA, Inc.*, 395 F.3d 1364 (Fed. Cir. 2005), *Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1369 (Fed. Cir. 2012), and *Hoffmann-La Roche, Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014),

as allegedly contrary is misplaced. None of these cases confines a patentee to the type of data in the patent specification in the obviousness inquiry. *Merck* is particularly instructive. The *Merck* claims covered once-weekly dosing of a drug, but the prior art suggested this dosing to avoid certain known, gastrointestinal side effects. *Id.* at 1368, 1373. The patentee nonetheless argued that skilled artisans would not have tried the dosing because of concerns about different side effects, but the patent did not claim avoidance of these side effects, and lacked data about them. *Id.* at 1373–74. The patent thus "add[ed] nothing beyond" the prior art's teaching of once-weekly dosing. *Id.* Here, in contrast, the patents teach that pure EPA will not increase LDL-C in severe hypertriglyceridemia (Appx86; Appx91), the prior art is concededly silent on that issue (Appx1398–1399 (Heinecke)), and the claims require the reduction of LDL-C. *Merck, Alcon*, and *Hoffmann-La Roche* say nothing about the facts of this case.

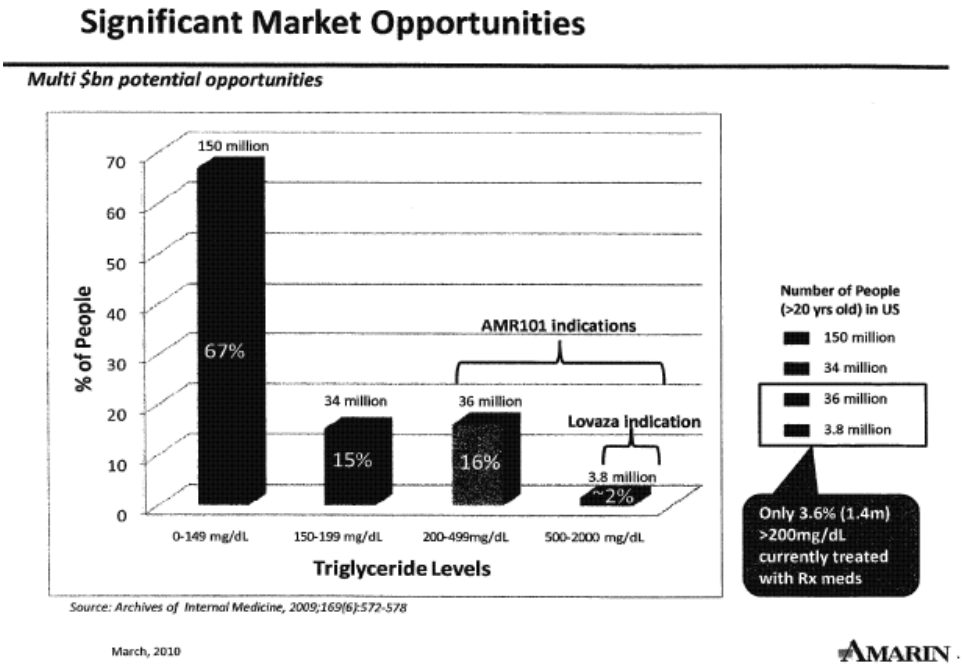
Next, Defendants essentially argue that a skilled artisan would have extrapolated from the non-severe population to the severe population because that is what Defendants say Amarin did. But that is the epitome of hindsight. *See Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012). In making their argument, Defendants ignore Amarin's evidence about Dr. Manku's development of the invention with an inexplicable suggestion of waiver and then use selected Amarin documents to cobble together a story that Amarin used the prior art to draw the same

conclusions that the Defendants want this Court to draw from it. These arguments twist the record until it is unrecognizable.

In its opening brief (at 18-21), Amarin explained Dr. Manku's insights and the data on which he relied to form his ideas about how EPA would work in treating severe hypertriglyceridemia. Amarin also explained the role clinical studies that Amarin's predecessor did on central nervous system disorders played in Dr. Manku's conception. (*Id.*) Defendants now argue (at 12 n.1) that Amarin somehow waived use of this evidence because they say it was "not disclosed in discovery." But the evidence comes directly from the deposition of Dr. Manku ***that Defendants elicited*** and that was presented at trial. Amarin's documents produced in discovery also show that Amarin relied on data from those central nervous system studies in seeking FDA approval for VASCEPA®. (Appx43744–43747.) Defendants' waiver argument is specious.

Of similar quality is Defendants' story about Amarin's development of VASCEPA®. While casually (and repeatedly) accusing Amarin of "misrepresentation" and "mischaracterization," Defendants pointedly omit from their tale that Amarin planned from the beginning (and ultimately conducted) multiple clinical studies simultaneously to obtain FDA approval for VASCEPA® in different patient populations with different triglyceride levels. (Appx44226; Appx90294.) In addition to seeking approval to treat patients with severe hypertriglyceridemia for the risk of pancreatitis, Amarin also sought approval to treat the much larger group of

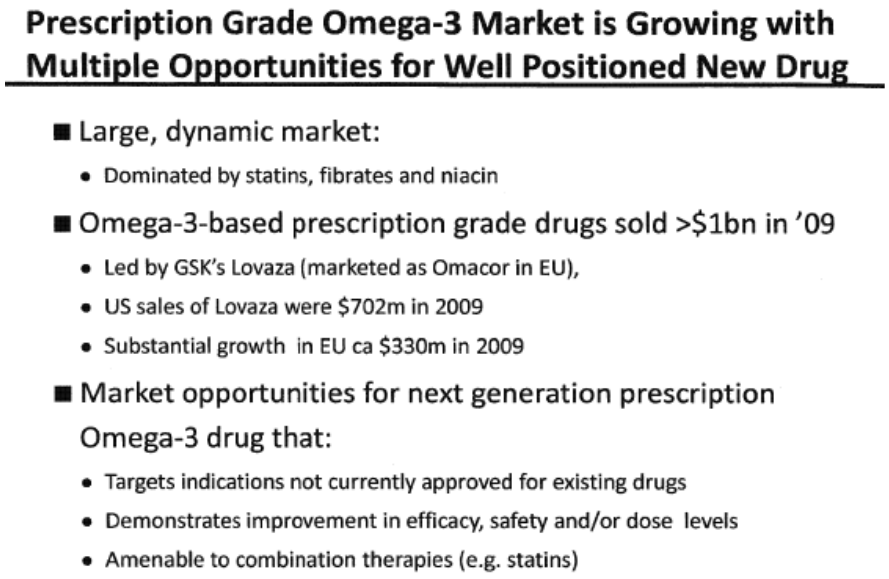
patients with elevated triglycerides to reduce their cardiac risk. (Appx90896; Appx90260–90261; *see also* Appx109974; Appx571–573 (Ketchum).) Amarin's 2010 presentation to its investors, on which Defendants heavily rely, vividly depicts the ten-fold difference in size of the two markets:



(Appx90248.)

As one might expect in a presentation designed to encourage investment, the presentation focused on the much larger cardiovascular indication. The presentation is titled, "Next Generation Lipid Modification in ***Cardiovascular Disease***" (Appx90245) (emphasis added), and states that Amarin's clinical plans "target[] indications not currently approved for existing drugs," i.e., indications that were

different than, for example, Lovaza®'s approved indication for treating severe hypertriglyceridemia:



Prescription Grade Omega-3 Market is Growing with Multiple Opportunities for Well Positioned New Drug

- Large, dynamic market:
  - Dominated by statins, fibrates and niacin
- Omega-3-based prescription grade drugs sold >$1bn in '09
  - Led by GSK's Lovaza (marketed as Omacor in EU),
  - US sales of Lovaza were $702m in 2009
  - Substantial growth in EU ca $330m in 2009
- Market opportunities for next generation prescription Omega-3 drug that:
  - Targets indications not currently approved for existing drugs
  - Demonstrates improvement in efficacy, safety and/or dose levels
  - Amenable to combination therapies (e.g. statins)

(Appx90250.)

Defendants' assertion (at 46) that "Amarin's statements [in this presentation] were all in the context of the '>500 mg/dL population being targeted initially' for [VASCEPA®'s] FDA approval" is thus flat-out untrue. Rather, those statements were "all in the context" of the "target[ed]" <500 mg/dL population. Indeed, at the time, Amarin knew that, although the FDA had only approved Lovaza® for severe hypertriglyceridemia, doctors frequently prescribed it to patients with triglycerides from 200-499 mg/dL, so much so that Amarin considered Lovaza® to have a "Supplemental Indication" in that population. (Appx90208.) During the relevant period, the Lovaza® label even contained clinical data from a study on those patients. (Appx44323.) Because these data showed a small rise in LDL-C, Amarin might have

a competitive advantage if it could show that its product would be LDL-C-neutral in this large group of patients, so it included data showing EPA's published effect on LDL-C in those patients in the presentation, including the data Defendants (at 15) copy in their brief. (Appx90256–90257; Appx90252 (EPA "LDL-C neutral in mixed dyslipidemia population").) Notably, the presentation lists the baseline triglycerides of the patients tested, none of which were over 260 mg/dL. (Appx90257.)

Similarly, for the 2008 documents on Epadel®, Amarin noted that the patient populations "typically had normal or mildly/moderately high triglyceride levels at baseline" and that "[n]one of the studies were in patients with very high triglycerides thus making direct comparisons to data from Lovaza studies difficult." (Apps90429.) And as for the FDA, Amarin absolutely told it in 2008 that "[i]n clinical studies performed with Ethyl-EPA to date … there is no evidence of a significant rise in LDL-cholesterol." (Appx90379–90381 at Appx90381.) But emblematic of their re-telling, Defendants (at 14) omit the very next sentence, which states "[h]owever, there have been no controlled studies of highly-purified Ethyl-EPA in patients with severe hypertriglyceridemia, the group most susceptible to marked rises in LDL-cholesterol induced by Lovaza." (Appx90381.)

Far from extrapolating from the lower population to the severe population, Amarin relayed the science accurately. Amarin relied on the prior art in the lower population because it was pursuing FDA approval in that population. (Appx600–606.) Defendants' fanciful tale is unmoored from what actually happened.

Lastly, Defendants (at 42, 49) try to suggest that the LDL-C increase in severe hypertriglyceridemia patients only happens well above 500 mg/dL, and that no such LDL-C surge would have been expected to occur at exactly 500 mg/dL, the only thing they say matters. But this argument is also unsupported. The Lovaza® label's warning about significant LDL-C increases is not limited to patients with triglycerides far above 500; rather, it is on the label for the ***entire population*** for which the drug is approved—severe hypertriglyceridemia patients with triglycerides ***starting at 500 mg/dL***. (Appx44323.) Notably, the experts Amarin consulted with in developing VASCEPA® specifically advised Amarin "to be very careful about patients on the threshold of 500mg/dL" because of the potential for the treatment "pushing up LDL-C." (Appx47720.)

Without any record support for this argument, Defendants (at 49) blatantly crop a quote from Amarin's brief to suggest that Amarin agreed that no rise in LDL-C would have been expected for patients with triglycerides of 499 mg/dL, and that since 500 is indistinct from 499, there would be no expectation of an LDL-C increase at 500 mg/dL either. But Amarin was contrasting the effects of triglyceride-lowering drugs in the different ***populations*** recognized in the art, noting that, in contrast to the patient population of 500 mg/dL or greater, the "sharp rise in LDL-C generally was not observed in patients with only borderline high (150-200 mg/dL) or high (200-499 mg/dL) triglycerides." (Blue Br. at 8.) These are the ***populations*** that the art recognized. (Appx49988–49990.) Thus, a skilled artisan would not have considered a

patient with exactly 500 mg/dL triglycerides to have had merely "high triglycerides" simply because her triglycerides were only one higher than 499, but rather would categorize her as having severe hypertriglyceridemia. (*Id.*) With this categorization came the understanding that reducing such a patient's triglycerides would likely lead to a large rise in LDL-C.

This argument is typical of Defendants' case—picking and choosing amongst the art's conclusions, always with hindsight, and is too clever by half. It flatly contradicts their story on motivation, which rests on the skilled artisan being motivated to eliminate Lovaza®'s observed LDL-C increases in the severely hypertriglyceridemic population, i.e., patients at "exactly" 500 mg/dL and above. It then moves the goalposts on reasonable expectation of success to whether a single patient with triglycerides of "exactly" 500 mg/dL—and not the population ≥500 mg/dL—might actually experience a LDL-C rise. Defendants (and the district court) cannot have it both ways—if motivation is based on a population effect, so must reasonable expectation of success. *See Institut Pasteur*, 738 F.3d at 1346 (expectation of success analysis must "match" the motivation, not switch to a different goal). Defendants' flip-flopping does nothing to fix the absence of evidence for the district court's extrapolation. The district court should be reversed.

III. None of Defendants' Alternative Grounds Merit Affirmance

A. The District Court Properly Found Infringement

Neither of Defendants' challenges to the district court's infringement judgment has merit. On the 12-week issue, Defendants' labels are indicated for treatment of severe hypertriglyceridemia, which is "generally a chronic condition caused by genetics" that "requir[es] long-term treatment." (Appx48; Appx913–938; Appx91137–91139; Appx1274–1276; Appx1294–1297.) According to the testimony of both sides' experts, the "Indication and Usage" section of Defendants' labels are directed not only to reducing triglycerides, but to maintaining that reduction, and that if a physician stops prescribing the drug, "in most cases [triglyceride levels] will go back up[.]" (Appx 47; Appx914–915; Appx925–Appx926; Appx1083–1085; Appx1271–1274; Appx1857–1858.) The "Clinical Studies" section of Defendants' labels further states that the patients in the supporting study were treated "for 12 weeks," only reporting results "at 12 weeks, not earlier." (Appx 48; Appx4436–4438; Appx95783–95784; Appx95828–95829.) Consistent with this labeling, both sides' physician experts testified that they generally prescribe VASCEPA® for either four or twelve months. (Appx1262; Appx1271.)

There was thus ample evidence for the district court's conclusion that Defendants' labels encouraged use of the product for "at least twelve weeks." Similarly, there was detailed support for the district court's finding of infringement on claims requiring administration of EPA without concurrent lipid-altering therapy.

Defendants' indication shows that FDA approved EPA as monotherapy—the labeling thus instructs that EPA is safe and effective by itself, without the need to prescribe another drug. (Appx52–53; Appx956–962; Appx2049–2053; Appx95777; Appx95821–95822; Appx4407–4409.) And the clinical studies on the label show that it is in fact administered alone 75% of the time. (Appx52–53; Appx2030–2031; Appx95783–95784; Appx95828–95829.)

Defendants' contrary arguments rest on a misapplication of law. Defendants argue that because the labels do not explicitly say physicians must administer EPA for 12 weeks or as monotherapy, the infringement findings must be set aside. But the burden to show induced infringement is not so high; rather, ". . . where a proposed label does not explicitly track the language of a claimed method, a package insert containing directives that will 'inevitably lead some consumers to practice the claimed method' provides sufficient evidence for a finding of specific intent." *Sanofi v. Glenmark Pharms. Inc., USA*, 204 F. Supp. 3d 665, 673–74 (D. Del. 2016), *aff'd sub nom. Sanofi v. Watson Labs. Inc.*, 875 F.3d 636 (Fed. Cir. 2017) (quoting *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010)). Defendants' labels do not need to say "prescribe for at least 12 weeks" or "administer without concurrent lipid-altering therapy." The district court found these implications clear, given the evidence cited above. (Appx47–49.)

None of Defendants' cited cases apply. Both *Grumenthal* and *Takeda* involve labels that ***carved out*** the patented indication, so naturally nothing in their labels

"encourage[d], recommend[ed], or promote[d] infringement." *Takeda Pharms. U.S.A., Inc. v. W.-Ward Pharm. Corp.*, 785 F.3d 625, 630 (Fed. Cir. 2015); *Grunenthal GMBH v. Alkem Labs. Ltd.,* 919 F.3d 1333, 1340 (Fed. Cir. 2019). *Horizon* is similarly distinguishable. There, the patented method involved three steps: (1) apply a medicated lotion; (2) wait for it to dry; and then (3) apply sunscreen, bug spray, or another medicated lotion. *HZNP Meds., LLC v. Actavis Labs. UT, Inc.*, 940 F.3d 680, 702 (Fed. Cir. 2019). The label at issue, however, instructed patients only to do the first step and warned that, ***if*** the user wanted to cover the affected area with anything else, ***then*** she should wait until the area was dry. But nothing in the label encouraged patients to actually cover the affected area with anything, much less the medications required by the claims. *Id.*

Here, Defendants' labels affirmatively instruct physicians that EPA is safe and effective as monotherapy to reduce triglycerides in severe hypertriglyceridemia and maintain that reduction long-term, and provide supporting clinical data after 12 weeks of EPA administration, largely in the absence of statins. The district court's infringement finding was proper.

B. Defendants' Alternative Invalidity Arguments Are Waived

Defendants wrap up by raising two short alternative invalidity arguments. Both are waived; neither has merit.

First, Defendants argue that the seven asserted claims not expressly excluding use of a statin would have been obvious over the use of EPA with a statin to

counteract any increase in LDL-C. Because their expert testified in no uncertain terms that his prior art combination was four references—Mori, Lovaza®, Hayashi, and Kurabayashi (Appx1317–1318)—and their pretrial filing also focused only on that single combination (Appx111621), this argument is waived. But even if not, it is inconsistent with the claims. To add anything as an alternative argument, Defendants must assume that EPA would have been expected to raise LDL-C. But the claims require that EPA "effects" a reduction in triglycerides ***without*** increasing LDL-C. (*E.g.*, Appx183–184.) Even if they allow for concurrent statin administration, they do not permit ***EPA*** to raise LDL-C. Moreover, if a skilled artisan believed a statin would be needed with pure EPA as well, there was no motivation to modify Lovaza®, let alone modify it to eliminate the DHA (which Mori prefers). (Appx88487; Appx2403–2405.) Defendants' alternative obviousness challenge fails.

As to Defendants' written description defense, the district court properly granted summary judgment that the late disclosure in four paragraphs of Defendants' reply expert report warranted preclusion of the defense at trial as a Rule 37(c)(1) discovery sanction. (Appx103437–103440.)

This Court reviews Rule 37(c)(1) sanctions under regional circuit law, and the Ninth Circuit reviews this issue for abuse of discretion, giving district courts "particularly wide latitude." *Tokai Corp. v. Easton Enters., Inc.*, 632 F.3d 1358, 1364–65 (Fed. Cir. 2011). In its detailed analysis of Defendants' misconduct, the district court

noted that Defendants had a "two month extension of the deadline to exchange their opening expert report . . . 'before committing to a final position on invalidity,'" and yet failed to disclose a written description defense until reply. (Appx103439.) Defendants also did not "argue their failure to disclose was substantially justified or harmless, instead focusing on the merits of a potential written description defense." (Appx103439–103440.) In light of this, the district court properly precluded the defense.

As at the district court, Defendants (at 63-64) argue the merits of written description as purportedly a "legal" issue that does not require expert testimony. But their own expert acknowledged that the patented field invokes a high level of skill (Appx105615), thus requiring expert testimony. *See Proveris Sci. Corp. v. Innovasystems, Inc.*, 536 F.3d 1256, 1267 (Fed. Cir. 2008). And even if expert testimony is not required in every instance that does not mean it's irrelevant. While the patents have *in haec verba* support for the claims, Amarin was prejudiced by not having the chance to present affirmative expert testimony to counter Defendants' arguments and explain the patent specification. The district court thus did not abuse its discretion in precluding Defendants from raising the issue at trial.

Dated: June 26, 2020

Respectfully submitted,

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CERTIFICATE OF SERVICE AND FILING

I hereby certify that I electronically filed the foregoing document with the Clerk of the Court of the United States Court of Appeal for the Federal Circuit by using the Court's CM/ECF filing system.

I certify that all participants in the case are registered CM/ECF users and that all counsel were served via CM/ECF on June 26, 2020.

/s/ Jonathan E. Singer
Jonathan E. Singer

CERTIFICATE OF COMPLIANCE

The undersigned attorney certifies that the opening brief for Appellants Amarin Pharma, Inc. and Amarin Pharmaceuticals Ireland Limited, complies with the type-volume limitation set forth in Fed. R. App. P. 32(a)(7)(B). The relevant portions of the brief, including all footnotes, contain 6,999 words as determined by Microsoft Word.

Dated: June 26, 2020

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