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' OPENING BRIEF

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May 12, 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.)

Dated: May 12, 2020

/s/ *Jonathan E. Singer*

cc: counsel of record

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STATEMENT OF RELATED CASES

In *Amarin Pharma, Inc. v. Dr. Reddy's Labs., Inc.*, 2:18-cv-01596-MMD-NJK (D. Nev.), which involves the same patents-in-suit, the district court issued a consent judgment based on the judgment in this case on May 4, 2020.

STATEMENT OF JURISDICTION

The district court had subject matter jurisdiction over these patent infringement cases under 28 U.S.C. §§ 1331 and 1338. The district court entered its final judgment on March 30, 2020. (Appx1–71.) Appellants timely filed their notice of appeal on April 2, 2020.

This Court has jurisdiction over the appeal under 28 U.S.C. § 1295(a)(1).

STATEMENT OF THE ISSUES

1. Whether the district court legally erred in its framework for evaluating objective indicia of non-obviousness, by (a) concluding that the claims were obvious before even analyzing the compelling objective indicia evidence, infusing its entire analysis with hindsight; and (b) improperly requiring Amarin to prove every objective indicia or have it count *against* non-obviousness.

2. Whether the district court improperly applied a hindsight-based analysis on motivation to combine and reasonable expectation of success, causing it to ignore significant evidence cutting against Defendants' case and shift the burden to Amarin to prove non-obviousness in an erroneous attempt to fill the evidentiary gaps in Defendants' proof.

INTRODUCTION

The phrase "hindsight is twenty-twenty" is a cliché for a reason. To guard against it, the Supreme Court and this Court require that district courts rigorously apply each of the *Graham* factors, including the common sense objective indicia, ***before*** declaring an invention obvious. Similarly, other concepts like a motivation to combine and reasonable expectation of success exist to avoid a hindsight reconstruction of the claims years after the fact. Because that which might appear obvious in hindsight often was not obvious at all.

In this case, the district court failed to follow these rules and, consequently, fell victim to hindsight. For decades, physicians treated severe hypertriglyceridemia, a genetically-based, life-threatening condition characterized by triglyceride levels of at least 500 milligrams per deciliter (mg/dL), with various medications that all dramatically raised LDL cholesterol ("LDL-C," the so-called "bad" cholesterol), thereby increasing patients' risk of cardiovascular disease. Whatever the treatment, the results were the same—while patients with milder forms of hypertriglyceridemia did not experience substantial LDL-C rises, those with severe hypertriglyceridemia saw dramatic increases in LDL-C.

Amarin's VASCEPA® solved this long-felt need. VASCEPA® is a 4g dose of pure eicosapentaenoic acid ("EPA"), an omega-3 oil. In clinical trials, VASCEPA® lowered triglycerides in patients with severe hypertriglyceridemia, but ***without*** raising

LDL-C. Upon FDA approval in 2012, VASCEPA® thus became the first (and still only) approved severe hypertriglyceridemia medication that does not raise LDL-C.

These issues were largely undisputed at trial. Defendants' expert acknowledged that an ordinary artisan would have understood, at the time of the invention, "that somewhere above 500 milligrams per deciliter the system for clearing triglycerides jams up," thus leading to the problem in the art. And, despite opining Amarin's patents were obvious over the prior art, that same expert conceded: "I don't think there's any evidence in the prior literature about what the impact of EPA would be on LDL cholesterol in patients with triglycerides above 500 milligrams per deciliter."

Nonetheless, the district court found the patents-in-suit obvious based on prior art about EPA that had been known for nearly a decade or more, none of which had led skilled artisans to solve the long-felt need met by VASCEPA®. In so doing, the district court put the cart before the horse, finding that "defendants have satisfied their burden" to provide "clear and convincing" evidence of obviousness (prima facie and otherwise) before even considering the proven objective indicia of long-felt need and commercial success. Even then, the district court improperly weighed these two proven objective indicia against those the district court decided Amarin had not proven, as if Amarin's alleged failures to prove praise or skepticism carried independent evidentiary weight. Under this Court's precedent, they do not.

These errors of hindsight were equally as serious in the district court's prima facie case. In analyzing motivation to combine and reasonable expectation of success,

the district court conflated patients without severe hypertriglyceridemia with those with the "jam[med] up" triglyceride clearing system of severe hypertriglyceridemia. Compounding this error, the district court shifted the burden to Amarin to show that these patient groups were different, as opposed to requiring Defendants to prove, by clear and convincing evidence, that they were expected to be the same, inexplicably faulting Amarin for offering "no evidentiary support" for its contentions, despite the mountains of testimony and documents Amarin provided.

Simply put, for seventeen years before the invention, pure EPA had been approved in Japan and was known to lower triglycerides. And, for at least 13 years before the invention, the prior art informed skilled artisans that EPA, like other drugs, did not substantially raise LDL-C in patients ***without*** severe hypertriglyceridemia. Yet no one did what the Amarin inventors conceived—develop a treatment for severe hypertriglyceridemia that, unlike the other prior art treatments, did not raise LDL-C. Only hindsight would suggest that this invention was obvious. The district court's judgment should be reversed.

STATEMENT OF THE CASE

I. The Technology

A. Before the Patented Methods, Treating Patients with Severe Hypertriglyceridemia Resulted in Increased Risk of Cardiovascular Disease

This case generally relates to methods of treating patients who have very high levels of triglycerides in their blood. Triglycerides are lipids, or fats, that naturally exist in the body, and are an important energy source for our bodies. (Appx3; Appx2316–2317 at 1561:21–1562:21 (Toth).) However, when triglyceride levels are too high, serious health effects can follow. (Appx871–872 at 324:5–325:17 (Budoff).) Specifically, triglycerides can build up in the blood and clog arteries, ultimately leading to heart attacks and stroke. (*Id.*)

A person with elevated triglycerides has "hypertriglyceridemia." Not all types of hypertriglyceridemia are created equal, however. At the time of the invention in 2008, skilled artisans recognized three classes of hypertriglyceridemia, based on triglyceride levels in patients' blood: (1) borderline-high (150–199 mg/dL); (2) high (200–499 mg/dL); and (3) very high (≥ 500 mg/dL). (Appx49988–49992; Appx873–875 at 328:17–23 (Budoff); Appx1770 at 1122:5 (Fisher); Appx1438 at 839:9–21 (Heinecke).) These same classifications still exist today. (Appx2322–2333 at 1568:1–1569:24 (Toth); Appx4.)

A patient with "very high" triglycerides (≥ 500 mg/dL) has "severe hypertriglyceridemia"—a condition afflicting roughly 3.5 million Americans. (Appx4;

Appx2466 (Toth).) Unlike the other types of hypertriglyceridemia—which may be caused by an unhealthy lifestyle and poor diet—severe hypertriglyceridemia occurs primarily in patients who, because of their genetics, have extremely elevated levels of triglycerides. (*See e.g.*, Appx47–48 (severe hypertriglyceridemia is "generally a chronic condition caused by genetics"); *see also* Appx879–880 at 332:3–7, 333:17–20 (Budoff) ("Genetic[s] . . . that's the largest and most common cause of very high triglyceride[s]"); Appx1008 at 461:8–11 (Budoff); Appx2325–2326 at 1571:16–1573:25 (Toth); Appx43134; Appx48858.)

Patients with severe hypertriglyceridemia also face a critical, and more urgent, risk than the increased cardiac risk generally associated with high triglycerides: acute pancreatitis, an extremely painful and potentially deadly inflammation of the pancreas. (*See* Appx4; Appx49988–49992; Appx2321–2324 at 1567:2–22, 1569:17–1570:19 (Toth); Appx877–878 at 331:3–20 (Budoff); Appx571 at 72:4–13 (Ketchum).) Consequently, FDA has long recognized severe hypertriglyceridemia as a distinct condition from other forms of hypertriglyceridemia, the only form of the disease to warrant an indication under FDA standards. (Appx2320 at 1566:4–16 (Toth); Appx49988; Appx50675–50676; Appx50357.)

Before Amarin's invention, the approved treatments for reducing triglycerides in severe hypertriglyceridemia patients all resulted in the same, negative consequence:

significant increases in LDL-C.[1] (*See, e.g.*, Appx5 (explaining that "[o]ther treatments for severe hypertriglyceridemia dramatically increase LDL-C levels").) Like triglycerides, cholesterols are naturally existing lipids that can serve important functions. (*See* Appx3; Appx871–872 at 324:16–325:5 (Budoff).) But LDL-C, known as the "bad" cholesterol, "is most associated with heart attacks and strokes." (Appx871–873 at 325:2–326:12 (Budoff).) Thus, as with patients suffering from high triglycerides, patients who have high LDL-C are at increased risk for cardiovascular disease. (*Id.*; Appx4 ("elevated LDL cholesterol is a major cause of CHD"); Appx88292.)

Before the inventions of the patents-in-suit, doctors frequently prescribed LDL-C lowering statins to their patients with severe hypertriglyceridemia to address the LDL-C increases caused by their triglyceride-lowering medications. (Appx2352–2353 (Toth); Appx887–889 (Budoff).) While, at first blush, this might appear to solve the problem, essentially this is robbing Peter to pay Paul. For patients who can tolerate statins, using them to offset LDL-C increases caused by another medication is a poor use of the drug. (Appx2352–2353 (Toth).) Utilizing statins in this way can "burn[] up" the LDL-C-lowering capacity of statins simply to get back to the baseline

[1] LDL stands for "low-density lipoprotein" and is measured by the amount of cholesterol it carries, known as LDL cholesterol, or LDL-C. HDL stands for "high-density lipoprotein, and HDL cholesterol (HDL-C) is commonly known as "good cholesterol."

of where LDL-C was before the severely hypertriglyceridemic patient began taking the triglyceride-lowering drug. (*Id.*)

What was needed, then, was a real solution to this problem—how to treat patients with severe hypertriglyceridemia to reduce the potentially deadly risk of acute pancreatitis, without putting them at an increased risk for cardiovascular disease by increasing their LDL-C. (Appx2466–2470 (Toth); Appx67.) Amarin's inventors solved it.

B. The Prior Art Methods of Treatment for Severe Hypertriglyceridemia

1. Prior Approved Treatments Dramatically Raised LDL-C in Severe Hypertriglyceridemia Patients, But Not in Patients with Less Elevated Triglycerides

At the time of Amarin's invention, there were three FDA-approved drugs, or classes of drugs, for lowering triglycerides in patients with severe hypertriglyceridemia: (1) niacin (vitamin B-3), (2) fibrates, which are derivatives of fibric acid, and (3) Lovaza® (also known as Omacor®), a complex mixture derived from fish oil, which has two primary constituents, EPA and DHA (docosahexaenoic acid). (Appx2328–2330 at 1574:1–1576:15 (Toth); Appx887 at 340:12–17 (Budoff); Appx578 at 79:17–25 (Ketchum); Appx110064; Appx49778–49787; Appx43935–43942; Appx88408–88411; Appx44323–44324.) While these medications all effectively lowered triglycerides in severe hypertriglyceridemia patients, as the experts at trial agreed and the district court found, all also dramatically raised LDL-C in these same patients.

(Appx1450–1451 at 851:15–852:1 (Heinecke); Appx2328–2352 at 1574:1–1575:1, 1598:14–17 (Toth); Appx5.)

Critically, this 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. In fact, some of these treatments even ***lowered*** LDL-C levels in such patients, and none raised them substantially.

Niacin is the oldest drug used to treat severe hypertriglyceridemia. (Appx50257.) Since at least 1977, however, it was understood that using niacin to reduce triglycerides in severe hypertriglyceridemia patients led to substantial increases in LDL-C. (Appx110064–110070; Appx2329–2332 at 1575:2-1578:11 (Toth); *see also* Appx2573 at 1789:19–22 (Toth); Appx1450–1451 at 851:15–852:1 (Heinecke) (conceding that niacin raises LDL-C in severely hypertriglyceridemic patients).) One prior art reference described this finding as "of major clinical concern" because the rise in LDL-C was "sometimes quite substantial," and could be "quite atherogenic." (Appx107783.) By contrast, in patients ***without*** severe hypertriglyceridemia, physicians used niacin to ***lower*** both triglycerides and LDL-C. (Appx50257.)

The next class of approved drugs, fibrates, also showed differential LDL-C effects depending on a patient's triglyceride level. (Appx2332–2337 at 1578:12–1583:17 (Toth).) Fenofibrate (marketed as Tricor®) ***reduced*** LDL-C by 13.5% in patients with borderline-high triglycerides. (Appx43934–43950 at 43939–43940;

Appx108954.) And in patients with high triglycerides, fenofibrate did not result in a statistically significant increase in LDL-C. (Appx43939–43940.)

Fibrates acted much differently, however, in severely hypertriglyceridemic patients—those with triglycerides of at least 500 mg/dL. In those patients, fenofibrate increased LDL-C dramatically—by 49.2%. (Appx49340; *see also* Appx2336–2340 at 1582:11–1586:24 (Toth).)

The third FDA-approved drug, Lovaza®, behaved the same. In severe hypertriglyceridemia patients, LDL-C increased 45–50% after Lovaza® treatment, but only 4.5–7% in patients with much lower triglycerides around 275 mg/dL. (Appx48910–48911; Appx2341–2345 at 1587:4–1590:11 (Toth).)

2. The Large LDL-C Increase in Severe Hypertriglyceridemia Patients Was Understood to Result from the Mechanism of Triglyceride Clearance

The understood mechanism behind this phenomenon at the time of Amarin's invention—LDL-C surges for patients with severe hypertriglyceridemia compared to much smaller increases or even decreases for patients with less elevated triglycerides—was explained at trial by Amarin's expert, Dr. Toth. Numerous prior art references corroborated his testimony. (Appx2344–2351 at 1590:12–1597:13 (Toth); Appx44256–44258; Appx48848; Appx48910–48911; Appx43935–43936; Appx43939–43940; Appx107779.)

As noted above, both triglycerides and cholesterol are fats. As a result, neither triglycerides nor cholesterol are soluble in water, so they cannot travel in the aqueous

(or water-soluble) part of the blood. (Appx2316 at 1562:12-17 (Toth).) Rather, proteins called apolipoproteins surround and carry triglycerides and cholesterol for ultimate delivery to cells that need energy. (Appx871–873 at 324:5–9, 325:21–326:12 (Budoff); Appx2316–2317 at 1562:9–21 (Toth).)

Apolipoprotein B ("Apo-B") is the lipoprotein that carries triglycerides and cholesterol, and can be used as an additional predictor of cardiovascular risk. (Appx872 (Budoff); Appx2481 (Toth).) Apo-Bs start out as "very low density lipoproteins" (VLDL), rich in triglycerides, and with a relatively small proportion of cholesterol. (Appx2315–2320 at 1561:21–1563:3 (Toth).) As enzymes remove the triglycerides from the lipoprotein and break them down into fatty acids for use as fuel, the lipoprotein shrinks in size and becomes denser, with relatively more cholesterol and less triglycerides. (*Id.*) In this process, VLDL is first converted to "[i]ntermediate density lipoproteins" (IDL). (*Id.*) As the metabolism continues, these IDL particles are then converted to LDL (*Id.*; Appx872–873 at 325:10–326:12 (Budoff).)

The genetics of severe hypertriglyceridemia patients cause the triglyceride-rich VLDL particles to build up in their blood like a "logjam." (Appx49988; Appx2315–2320 at 1561:16–1566:3; Appx2325–2327 at 1571:16–1573:25 (Toth).) This genetically caused "logjam" manifests itself in dangerously high, sustained triglycerides of at least 500 mg/dL. This logjam was not disputed at trial—Defendants' expert Dr. Heinecke acknowledged that: "we knew [in 2008] that somewhere above 500

milligrams per deciliter the system for clearing triglycerides jams up." (Appx1395–1396 at 796:21–797:2 (Heinecke).)

While scientists continue to study their precise mechanisms of action even today, at the time of Amarin's invention, existing triglyceride-lowering treatments were all believed to break this logjam by activating the enzymes to convert the large volume of excess VLDL particles to LDL particles. As a consequence, large surges in LDL resulted, dramatically increasing LDL-C. (Appx2344–2351 at 1590:12–1597:13; Appx2315–2318 at 1561:16–1564:22 (Toth) ("But if you break that logjam and suddenly you activate the enzyme somehow, then you can see a large surge in the production of that LDL and the LDL[-C] levels would rise.").)

The prior art consistently reflected this understanding, whether it occurred with Lovaza®, fibrates, niacin, or even diet. For example, a 2008 article by Bays, et al. about Lovaza® stated:

> ***As with fibrates***, the degree of LDL-C elevations observed with [omega-3] treatment is ***generally related to the pretreatment TG levels***. [Omega-3 fatty acids] increase[] LDL-C levels the most in patients with the highest pretreatment TG levels. ***The reason for the increased LDL-C levels with [omega-3 fatty acids] is related to the increased conversion of VLDL particles to LDL particles***.

(Appx44247–44265 at Appx44256–44258[2]; Appx2350–2351 at 1596:11–1597:13 (Toth); *see also* Appx107779 (noting phenomenon even when triglycerides are lowered through diet in patients with severe hypertriglyceridemia).)

[2] All emphasis added unless noted otherwise.

Similarly, a 2007 clinical review by McKenney commented:

> ***As with fibric acid derivatives (fibrates) and nicotinic acid (niacin***), reductions in triglycerides and very-low-density-lipoprotein (VLDL) cholesterol [achieved by DHA and EPA] are generally greater in patients with higher baseline triglyceride levels. ***An 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***.

(Appx48844–48856 at Appx48848; *see also* Appx2345–2349 at 1591:12–1595:3 (Toth).) McKenney further observed that, under the influence of omega-3 fatty acids, "the conversion of VLDL to LDL particles increased 93%," explaining the rise in LDL-C in severe hypertriglyceridemia patients: "[t]he results also show that VLDL particles ***are rapidly converted to LDL particles, thus explaining why LDL cholesterol levels may rise in patients with very high triglycerides when given [omega-3 fatty acid] therapy***." (Appx48848.)

Skilled artisans thus did not consider the surge in LDL-C as a mere "side effect" of certain medications. Rather, they understood it as a function of the mechanism of clearing the triglycerides themselves, which, in patients with severe hypertriglyceridemia, malfunctions because of their genetics. (*See, e.g.*, Appx2344–2352 (Toth).)

Because of this surge, physicians generally had to prescribe a statin in an effort to negate the rise in LDL-C. In addition to the issue of "burning up" the statins' LDL-C lowering capacity, clinicians also recognized that patients are far less likely to take consistently two pills rather than just one—indeed, most patients stop taking

statins after six months. (Appx2352–2353 (Toth); Appx1412–13 at 813:8–814:2 (Heinecke).) Moreover, when a particular patient could not tolerate statins, there were limited options for addressing the dramatic rise in LDL-C. (Appx2352–2353 (Toth).)

Before 2008, there was thus a pressing need for a safe, well-tolerated treatment that could successfully reduce triglycerides in severe hypertriglyceridemia patients, thereby addressing the risk of pancreatitis, but ***without*** causing a surge in LDL-C and the corresponding increase in cardiovascular risk. (Appx2466–2470 (Toth); Appx67.)

3. The State of the Prior Art Relating to EPA

Before Amarin's inventors conceived their invention, others had used EPA to treat lipid disorders, but not for treating the severe hypertriglyceridemic population. For example, a pure EPA product known as Epadel® had been on the market in Japan since 1991. (Appx677; Appx88321–88334.) But Epadel® was not approved to treat severe hypertriglyceridemia. (Appx2427–2430 (Toth); Appx4151–4152 (Manku).)

Given EPA's prior long-standing use in Japan, there were many published clinical studies relating to treating hypertriglyceridemia with pure EPA before Amarin's invention. All involved patient groups that, on average, had either normal, borderline high, or high levels of triglycerides, but not severe hyperglyceridemia. Among these was the study relied on heavily by the district court in invalidating Amarin's patents, the Mori reference ("Mori") (Appx88480–88489).

Mori discloses a clinical experiment from 2000 that studied the separate effects of 4g of pure-EPA, 4g of pure-DHA product and an olive oil placebo in 56 patients with "***mild*** hyperlipidemia." (Appx88480.) As the experts at trial agreed, mildly hyperlipidemic patients have only modestly elevated triglycerides, i.e., under 200 mg/dL. (Appx1429–1430 (Heinecke); Appx1494–1495 (Heinecke); Appx2394–2395 (Toth).)

Mori reports that both DHA and EPA showed about the same triglyceride-lowering ability, roughly 20%. (Appx88483; Appx2398–2399 (Toth).) As to LDL-C, Mori reports DHA showed a small, but statistically significant rise (8%), while EPA showed a non-statistically significant increase (3.5%). (Appx88483; Appx2396–2397 (Toth).) Mori also reports DHA and EPA's effects on HDL, blood glucose, and LDL particle size, concluding that that "EPA and DHA had differential effects on lipids, fatty acids, and glucose metabolism in overweight men with mild hyperlipideimia."[3] (Appx88480.) As between the two, Mori expresses a preference for DHA: "[d]espite an increase in LDL cholesterol after DHA supplementation, the increased LDL particle size may represent a shift to less atherogenic particles, in which case the parallel increase in HDL cholesterol and decrease in triacylglycerol may represent a

[3] Regrettably, the district court presented Mori's conclusion without reference to Mori's mildly hyperlipidemic population as follows: "Mori concludes that 'EPA and DHA had differential effects on lipids.'" (Appx25.)

more favorable lipid profile than that seen after EPA supplementation." (Appx88487; *see also* Appx2403–2405 (Toth).)

While, at Defendants' urging, the district court seized on the LDL-C difference between DHA and EPA in Mori in assessing obviousness, Mori itself found it unremarkable. In fact, Mori comments about the ***rise*** in LDL-C observed in ***both*** groups and hypothesizes that it results, in part, from the same mechanism described in the literature discussed above—an increased conversion of VLDL to LDL:

> Although the LDL-Cholesterol concentration increased after EPA and DHA intakes, the increase was significant only after DHA. The increased LDL-cholesterol concentration may relate to the hypotriglyceridemic effects of these fatty acids. n-3 Fats reduce hepatic VLDL synthesis, VLDL secretion, or both with the result that the smaller VLDL particles formed are more readily converted to LDL than the larger VLDL particles.

(Appx88485.)

In this regard, Mori is typical of the prior art on EPA before Amarin's invention—studies showing a variety of effects of EPA on patient groups with moderately elevated, but not severely elevated, triglycerides. As Defendants' expert Dr. Heinecke conceded: ". . . I don't think there's any evidence in the prior literature about what the impact of EPA would be on LDL cholesterol in patients above 500mg per deciliter." (Appx1398–1399.)

Of a piece with Mori were two other Japanese references featured in the district court's opinion: Hayashi and Kurabayashi. (Appx88363–88372; Appx88400–88407.) Hayashi is a 1995 study of 28 patients with mean triglyceride levels of 300 mg/dL. In

the paper, 1.8 g of EPA lowered triglycerides, but without an increase in LDL-C. (Appx88366–88367; Appx2411–2412 (Toth).) And, while the district court found that Hayashi included at least one patient with triglycerides above 500 mg/dL, the experts agreed that Hayashi reported no LDL-C data for any patients with triglycerides above 400 mg/dL. (Appx1493–1494 (Heinecke); Appx2408–2413 (Toth).) Nor could it have, because, as the experts also agreed, Hayashi calculated LDL-C by the Friedewald equation, which is inaccurate above 400 mg/dL triglycerides. (Appx1398–1399 (Heinecke); Appx1493–1494 (Heinecke); Appx2412–2413 (Toth).)

Kurabayashi is even further afield. Kurabayashi is a year 2000 study comparing the effects of estrogen and estrogen plus 2g of EPA in 141 menopausal women. (Appx88400.) Both groups had ***normal*** average triglycerides, around 135 mg/dL. (Appx88403; Appx 1429 (Heinecke); Appx1495–1496 (Heinecke); Appx2415–2416 (Toth); Appx2432 (Toth).) Table 2 of Kurabayashi reports that triglycerides declined significantly in the EPA plus estrogen group, and went up non-significantly in the estrogen-only group, while LDL-C went down significantly in both groups. (Appx88403.) In addition, Table 3 shows that Apo-B went down significantly in the EPA plus estrogen group, but this finding was not significantly different from the

estrogen only group, where Apo-B declined only numerically.[4] (Appx88404.) Notably, Kurabayashi excludes any patients with triglycerides above 400 mg/dL. (Appx88401.)

Accordingly, at the time of the invention, no one had even thought to try the widely-studied EPA in a severely hypertriglyceridemic population before the Amarin inventors conceived that it would solve the problem that the art faced—namely, how to avoid the LDL-C surge caused by lowering triglycerides in patients with severe hypertriglyceridemia.

II. Amarin's Patented Method of Treatment

A. The Inventors Saw New Potential in an Old Product, and Conceived of Pure EPA as an Effective Treatment for Severe Hypertriglyceridemia That Avoided Increasing LDL-C

Against this background, Amarin developed its groundbreaking and successful treatment for severe hypertriglyceridemia. Rather than developing a new active ingredient, the inventors instead looked to the old ingredient that had been on the market in Japan for over 15 years—EPA. Their insight—contrary to the common wisdom of the time—was that pure EPA could effectively lower triglycerides in patients with severe hypertriglyceridemia ***without*** causing the typical surge in LDL-C.

[4] Unfortunately, in reprinting Table 3 of Kurabayashi's Apo-B results, the district court's opinion cut off the inter-group statistical comparison. (*Compare* Appx30 *with* Appx88404.) Defendants' proposed findings of fact did so as well. (Appx102826.)

This insight led to the patents-in-suit, embodied in Amarin's novel and life-saving drug, VASCEPA®.

Dr. Mehar Manku was the lead inventor on the project. He joined Amarin as Vice President of Research and Development in November 2004.[5] At the time, Amarin had roughly a dozen employees. (Appx775 (Ketchum).)

Before joining Amarin, Dr. Manku worked at Amarin's predecessor Laxdale, and, before that, had "work[ed] in the area of fatty acids as medicines for . . . almost 40 years or so and worked extensively using EPA." (Appx4142; Appx4121 (Manku).) At Laxdale, he studied the use of purified EPA for neuropsychiatric indications such as depression, schizophrenia, and Huntington's Disease. (Appx4128-4130, Appx4135-4137.) He brought this work with him to Amarin. And while the clinical trials on the neuropsychiatric conditions did not meet their endpoints, these trials nonetheless generated significant, non-public data. (Appx4136–4137, Appx4144–4146; Appx90356–90358; Appx43697–43699.)

These data keyed Dr. Manku into EPA's potential as a possible therapy for severe hypertriglyceridemia, knowing that the then-available treatments for that condition caused a significant rise in LDL-C and there was a need for a treatment option that did not. (Appx4190–4194; Appx4149–4151 (Manku); *see also* Appx2469–2471 (Toth).) This is because schizophrenia drugs usually drive large increases in

[5] Dr. Manku is a resident of Birmingham, England, and had retired from Amarin at the time of trial. (Appx4119; Appx4163.) He testified by deposition.

triglycerides, but the blood data from the neuropsychiatric clinical trials showed that administering EPA to these patients not only reduced triglycerides, but did so without raising LDL-C. (Appx4273–4275; Appx4206.) Digging deeper into these results, Dr. Manku gained significant insight about lipid blood levels and, importantly, about how EPA works in the body. (Appx4195–4204.) From these data, combined with his own knowledge, by 2007, Dr. Manku concluded that DHA—the other primary constituent of Lovaza®—"actually interferes with the mode of action of EPA." (Appx4197; Appx4162–4163.)

From this conclusion, Dr. Manku conceived that purified EPA by itself, without interference from DHA, could reduce triglycerides in severe hypertriglyceridemia without raising LDL-C. (Appx4120; Appx4243; Appx4159–4163.) He thus decided to study pure EPA for this purpose, even though, prior to that, no one had thought to look at "what would be the clinical benefit" of using pure EPA in patients "with very high triglycerides of over 500." (Appx4198–4199.)

Dr. Manku's colleagues at Amarin did not share his optimism. (Appx4251–4252.) As he testified, "all the experts that we were talking to" at the time of the invention were saying, "[l]ook there is LDL increase in over 500 patient population. It's a phenomena, you cannot stop it, it will happen because that is the physiological mechanism . . ." (Appx4252; Appx4221–4224 (explaining that "[t]he experts were not in favor of" his idea of using EPA in patients with very high triglycerides.) Dr. Manku sent his colleagues publications to try to convince them that "mechanism wise

this is going to be a different type of mechanism." (Appx4252.) But nonetheless, Dr. Manku had "great difficulty in convincing individuals within the company, and outside the company, on why ethyl-EPA would be effective in lowering triglycerides significantly in [the] very high patient population, with those over 500 [mg/dL], and would not affect other lipid parameters." (Appx4193.) Indeed, it took him a "long time" to convince them. (Appx4194.)

Dr. Manku used the insights gleaned from the neuropsychiatric clinical data, along with "bits and pieces of information, although not in the right population" from the prior art to help convince his colleagues that he was right. (Appx4273–4274; *see also* Appx44204–44205 (discussing EPA's effects in schizophrenia patients); Appx44069–44072 (explaining views on how EPA affects lipids and biomarkers); Appx44196–44203.) As the company's expert on omega-3 oils, Dr. Manku sent his colleagues examples of this information to "educate them about the literature that's available related to EPA." (Appx4245–4246.) He listened in on calls with potential investors and sent e-mails to colleagues to convince them that his insight was correct and that expensive clinical trials in patients with severe hypertriglyceridemia would not be a waste. (Appx4254; Appx4260–61.)

Those "bits and pieces of information" in the art showed that omega-3 fatty acids like EPA had some potential beneficial outcomes, as in Mori, Hayashi and Kurabayashi, but "[t]he direction and magnitude of change does vary from study to study depending on size, ***nature of population***, and duration of treatment, and dose

of [purified fatty acids]." (Appx90286–90288.) After convincing his colleagues, Dr. Manku worked with them, using the information that he provided, to develop the scientific rationale for the development project, ultimately meeting with FDA to help construct the clinical trials. (Appx4229–4230.)

B. Amarin's Clinical Trials on EPA Surprisingly Showed a Reduction in Triglycerides without a Corresponding Increase in LDL-C in Severe Hypertriglyceridemia Patients

Amarin moved forward with a clinical program to test pure EPA in severe hypertriglyceridemia patients beginning in late 2008. (Appx4193–4194 (Manku); Appx571–573 (Ketchum).) Before actually starting the trials, Amarin hosted a group of experts to get their views on the clinical trial design and the effects that EPA might have. (Appx43971; Appx43974–43977; *see also* Appx4985–4986.) In advance of the meeting, Amarin provided extensive materials to the experts, including a summary of information about prior art studies of EPA's effects on LDL-C, including Mori. (*E.g.*, Appx43970; Appx43986; Appx43992; Appx4276–4277.) Nonetheless, as reflected in contemporaneous notes from that meeting, these experts remained skeptical that EPA would reduce triglycerides in severely hypertriglyceridemic patients without substantially raising LDL-C: "LDL-C is likely to go up as it does with virtually all tg lowering therapies in this group of patients." (Appx47719–47722 at Appx47720; Appx4985–4992 (Osterloh).)

These experts turned out to be wrong. Amarin's MARINE clinical trial, which examined the effects of Amarin's purified EPA formulation on severe

hypertriglyceridemia patients, showed that 4g of EPA effectively reduced triglycerides by 33%, but without the typical surge in LDL-C. (Appx47963–Appx47964; Appx47929–47949; Appx594–596 (Ketchum); Appx2358–2360 (Toth).) In addition, 4g of EPA (though not 2g) surprisingly led to a 9% reduction in Apo-B. (Appx47937–47938.) The MARINE Clinical Study Report notes the difference between its results and the prior art treatments for this patient population: "[i]n contrast to other TG-lowering agents, the reduction in TG levels was not associated with an elevation in LDL-C levels compared to placebo." (Appx47870; *see also* Appx2358–2359 (Toth).)

Based on the MARINE study, FDA approved VASCEPA® on July 26, 2012 "as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia." (Appx43106; *see also* Appx50675–50688; Appx550–551 (Ketchum); Appx564 (Ketchum).) Upon approval, FDA publicly released a 2011 Medical Review, which detailed FDA's evaluation of Amarin's clinical data and the rationale for recommending FDA approval. (Appx601–602 (Ketchum); Appx43682–43689.)

The Medical Review identified the "Important Safety Issues" that FDA recognized in prior treatments, highlighting that "the only other FDA approved omega-3 fatty acid product (Lovaza)" has "four areas of potential safety concern," beginning with "increases in LDL-C." (Appx43686.) Consistent with the understanding in the art of the mechanism of reducing triglycerides in patients with

severe hypertriglyceridemia, FDA explained that "[t]he increase in LDL-C" observed with Lovaza® "is thought to be due to the . . . enhance[d] . . . conversion of [VLDL] and [IDL] to LDL-C." (Appx43686; *see also* Appx1460–1463 (Heinecke) (admitting that FDA "continued to believe" this was the mechanism for Lovaza® even in 2011).) The Review goes on to conclude: "Vascepa 4 g did not increase LDL-C levels," thus eliminating the "Important Safety Issue" of increased LDL-C. (Appx43729–43730.)

Even before its approval, when only preliminary, non-peer-reviewed results were available, clinicians recognized VASCEPA®'s ability to lower triglycerides in patients with severe hypertriglyceridemia while avoiding the surge in LDL-C that had plagued the prior art. (*See* Appx2360–2369 (Toth); Appx2476–2477 (Toth).) For example, a prominent cardiologist from the Cleveland Clinic described the early results as a "real advance in the treatment of elevated triglycerides" because "[i]t gives you all the benefit without the downside." (Appx86649–86651 at Appx86650; Appx2364–2366 (Toth); Appx2477 (Toth).) This same cardiologist hailed the results as showing that "[t]here's still room for small companies to do innovative things in this field." (Appx86650; *see also* Appx48698–48706 at Appx48702.)

Consistent with this early recognition, VASCEPA® has seen great success in the marketplace, with an average annual growth rate of 54% since launch and net sales of $226 million in 2018. (Appx39–42; Appx2124; Appx2127–2129 (Nicholson).) But Amarin did not sit back and simply reap the profits. Instead, Amarin poured much of the revenues from VASCEPA® sales into further clinical research. In a study of over

8000 patients over five years called REDUCE-IT, Amarin evaluated the effectiveness of VASCEPA® as an add-on to statin therapy in reducing major cardiovascular events in patients with more moderately elevated triglycerides. (Appx50691–50709; *see also* Appx639–640 (Ketchum).)

The results of REDUCE-IT, first announced in 2018, were an additional great advance for cardiovascular health. Compared to statins alone, VASCEPA® showed a 25% reduction in major cardiovascular events. (Appx50819–50825; Appx2370–2373 (Toth).) Based on those results, in December 2019, FDA approved VASCEPA® for a second indication as an add-on to statin therapy to reduce the risks of heart attacks, strokes and other cardiovascular events in certain patient populations. (Appx50675; Appx38.)

In a press release about this additional approval, FDA recognized that "VASCEPA is the first FDA-approved drug to reduce cardiovascular risk among patients with elevated triglyceride levels as an add-on to maximally tolerated statin therapy." (Appx50672–50673; *see also* Appx2379 (Toth); Appx1450–1451 (Heinecke).) The results of REDUCE-IT have understandably been met with widespread enthusiasm in the field. (Appx2377–2387 at 1625:22–1633:5 (Toth); Appx49765–49766; Appx48717–49719; Appx47464–47492; Appx49004–49006; Appx48737–48737; Appx660 (Ketchum).)

C. Amarin's Patents-in-Suit Claim Its Invention of Treating Severe Hypertriglyceridemia without Raising LDL-C

Amarin's six patents-in-suit cover its innovative methods of treatment of using pure EPA to treat severe hypertriglyceridemia. (Appx72–207.) The ten claims asserted at trial generally cover methods of reducing triglycerides in patients with severe hypertriglyceridemia without raising LDL-C levels by administering pure EPA. Claim 1 of the '728 patent is representative:

> A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl who does not receive concurrent lipid altering therapy comprising: administering orally to the subject about 4 g per day of a pharmaceutical composition comprising at least about 96%, by weight of all fatty acids present, ethyl eicosapentaenoate, and substantially no docosahexaenoic acid or its esters for a period of 12 weeks to effect a reduction in triglycerides without substantially increasing LDL-C compared to a second subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl who has not received the pharmaceutical composition and a concurrent lipid altering therapy.

(Appx92.)

During prosecution of its patents, Amarin cited each of Mori, Hayashi, and Kurabayashi. (Appx73–80.) In allowing Amarin's first patent, the '728 patent-in-suit, the Examiner focused on the most important aspect of Amarin's invention—that by using 4g of pure EPA to treat severe hypertriglyceridemia, the inventors filled the long-felt need for a severe hypertriglyceridemia treatment that did not result in elevated LDL-C. (Appx57815–57821 at 57820.) The Examiner also commented

favorably on the surprising reduction in Apo-B that Amarin's invention achieved, as demonstrated in the MARINE clinical trial. (Appx57818–57819.)

III. The Present Litigation

VASCEPA®'s success attracted potential generic competition. On the four-year anniversary of FDA approval, each of the two generic Defendants in this case—Hikma and Dr. Reddy's—filed abbreviated new drug applications seeking FDA approval to market generic versions of VASCEPA®. (*See* Appx5; Appx7–10.)

After receiving paragraph IV letters from each of the Defendants, Amarin filed suit against both for patent infringement in the District of Nevada. (Appx1–2.) Defendants answered, asserting non-infringement and invalidity. (Appx2.) On summary judgment, the district court ruled that defendants had waived any challenge to the patents-in-suit under 35 U.S.C. § 112. (Appx103437–103440.) The district court then held a seven-day bench trial in January 2020 to resolve infringement and obviousness. (*See* Appx1.)

On infringement, Defendants' primary argument was that their labels would not induce infringement because, according to them, the labels did not instruct doctors to administer EPA for at least 12 weeks, as required by all the claims. (*See generally* Appx102740–Appx102744.) The district court correctly rejected this argument, explaining that the evidence at trial "established that severe hypertriglyceridemia generally has a genetic component, meaning that it is usually a chronic condition requiring long-term treatment." (Appx47–48.) Thus, as the district

court found, if approved, Defendants' labels would induce infringement of this limitation, as well as the other limitations Defendants challenged, which, in the main, related to not raising LDL-C and lowering Apo-B. (Appx47–54.)

Where the district court went wrong, though, was in its analysis and conclusions with respect to obviousness. At trial, Defendants asserted that the challenged claims would have been obvious over four "key" references: (1) a physician's desk reference ("PDR") for Lovaza® ("Lovaza® PDR"); (2) Mori; (3) Hayashi; and (4) Kurabayashi. (Appx1317–1318 (Heinecke); Appx102745–102750; Appx102820–102826; Appx103349–13351.) According to Defendants, a skilled artisan would have modified the Lovaza® PDR method—treating severe hyperglyceridemia with a mixture of components that included EPA and DHA—to using only EPA because Mori, Hayashi and/or Kurabayashi made it obvious that EPA would not increase LDL-C in patients with severe hypertriglyceridemia, unlike Lovaza®. (*See, e.g.* Appx103349–103351; Appx56–61.)

Defendants' theory was, and is, pure hindsight. While it may seem obvious in 2020 that using EPA alone would treat severe hyperglyceridemia without raising LDL-C after Amarin had already figured it out, no one else had figured this out during the nearly two decades leading up to the time of the invention, when an approved EPA product was on the Japanese market. (*See, e.g.*, (Appx677; Appx88326–88334; Appx4151–4152 (Manku); Appx1488–1489 (Heinecke).) Even the question Defendants framed for the district court to consider—that a skilled artisan would

investigate Lovaza® to determine whether DHA or EPA or both caused LDL-C to increase—was based on hindsight. (*See e.g.*, Appx103349–103350; Appx57.) Only someone who knew the answer would ask the question this way, instead of believing that the disease itself was responsible for the increase.

The district court fell victim to this hindsight. Unfortunately, the court adopted a framework for analyzing obviousness that this Court has cautioned against and that can lead to hindsight—first considering a "prima facie" case of obviousness before weighing objective indicia such as the long-felt but unmet need for a product like VASCEPA®. Specifically, in its legal analysis, the district court found 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; *see also* Appx59 ("The Court therefore finds that Defendants established by clear and convincing evidence at Trial that all Asserted Claims are *prima facie* obvious.").) Only after this did the district court consider the objective indicia, requiring them to "overcome" the prima facie case of obviousness. (*See* Appx69.)

With regard to the purported prima facie case, in finding that a skilled artisan would have been motivated to modify the treatment of the Lovaza® PDR in line with Defendants' theory, the district court conflated the severely hypertriglyceridemic patient population in the Lovaza® PDR with the more mildly afflicted populations in Mori, Hayashi, and Kurabayashi. (Appx57–61.) In so doing, the district court: 1) ignored the extensive testimony and publications about why drugs might cause a

dramatic rise in LDL-C in severe hypertriglyceridemia, while not causing it in milder conditions; 2) failed even to mention the differing effects of Lovaza® and fibrates in the two populations; and 3) dispensed with evidence on niacin's differential effects as being "from 1977" despite general agreement on these effects. (Appx60.)

The district court's analysis of reasonable expectation of success was no better. Based on nothing more than the conceded fact that a skilled artisan would expect triglyceride-lowering drugs to lower triglycerides in patients above 500 mg/dL, as they had below 500 mg/dL, the district court asserted that Amarin's contentions about the differential LDL-C rise "lack[ed] evidentiary support," despite the evidence discussed above. (Appx60.) In a passage of the opinion strikingly copied verbatim from Defendants' proposed findings (*compare* Appx60–61 *with* Appx102950), the district court even faulted Dr. Toth for "cit[ing] no evidence that the 500 mg/dL threshold reflects any difference in how patients metabolize drugs, or any relationship between that specific threshold and LDL-C." (Appx60.) Putting aside that Dr. Toth presented lengthy testimony on this issue, backed up by the prior art (Appx2328–2352 (Toth); Appx110064–110070; Appx43934–43950; Appx48910–48911; Appx44247–44265; Appx48844–48856), it was not Amarin's burden to prove this difference—rather, it was Defendants' burden to prove that skilled artisans would reasonably expect a lack of one. They utterly failed to do so.

Equally flawed was the district court's consideration of the objective indicia. For one, despite crediting Amarin's evidence of a long-felt but unmet need and

commercial success, the district court found that "these secondary considerations [were] outweighed by the fact that the Court found Plaintiffs' other proffered secondary considerations favor Defendants"—in essence finding that Amarin would have been better off had it not presented evidence concerning these other objective indicia. (*See* Appx69.) As to those other indicia, the district court: 1) wrote off powerful evidence of skepticism based on an apparent and erroneous belief that those expressing skepticism were not aware of Mori (Appx67–68); 2) wrongly rejected evidence of praise from independent physicians as too "qualified and equivocal" merely because the doctors were cautious about interpreting early results that had not yet been peer reviewed (Appx68–69); and 3) erroneously discounted Amarin's evidence of unexpected benefits because the court wrongly thought that Kurabayashi had not been cited to the patent office (Appx66).

To remedy these errors in the district court's obviousness analysis, Amarin now appeals.

SUMMARY OF THE ARGUMENT

The district court's obviousness judgment suffers from fundamental errors. First, the district court erroneously bifurcated a "prima facie" case of obviousness and the objective indicia of non-obviousness. By so doing, the district court fell into the trap of hindsight—dismissing powerful objective evidence of non-obviousness because the court had already decided the claims were obvious. Compounding this error, the district court inexplicably "weighed" the objective indicia that the court ruled Amarin had proven against those that it ruled Amarin had not. When the objective indicia receive proper weight, Amarin's claims are plainly non-obvious.

Hindsight also infected the district court's analysis of the prima facie case. Before Amarin's invention, all prior treatments for severe hypertriglyceridemia had the same effect—a dramatic rise in LDL-C—not seen in patients with milder forms of the disease. The district court disregarded this key difference, never even explaining the underlying science of the disease. In the process, the court improperly shifted the burden to Amarin, requiring it to prove that triglyceride-lowering drugs produced different effects depending on patients' baseline triglyceride levels. And while Amarin did just that, the end result of the district court's analysis was an obviousness judgment that effectively ruled that ordinary artisans had a reasonable expectation of producing that which had never been achieved before Amarin's inventions—a triglyceride-lowering therapy for severe hypertriglyceridemia that did not dramatically raise LDL-C. The district court should be reversed.

STANDARD OF REVIEW

"Obviousness is a question of law based on underlying factual findings." *In re Cyclobenzaprine*, 676 F.3d 1063, 1069 (Fed. Cir. 2012). When reviewing a district court's obviousness judgment after a bench trial, this Court "review[s] its legal conclusions de novo, but [] review[s] its underlying factual findings for clear error." *Id.* at 1069.

ARGUMENT

I. The District Court's Obviousness Judgment Should Be Reversed.

A. Hindsight Bias Infected the District Court's Analysis of Objective Indicia

As this Court has repeatedly recognized, careful consideration of objective indicia of non-obviousness serves as an important "guard against slipping into the use of hindsight" and disciplines courts to "to resist the temptation to read into the prior art the teachings of the invention in issue." *Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1052 (Fed. Cir. 2016) (en banc) (internal quotation marks omitted). Indeed, objective indicia "may often be the most probative and cogent evidence in the record." *Ortho–McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008). This is because the objective indicia often provide an "unbiased indication" as to "how the patented device is viewed in the marketplace, by those directly interested in the product"—rather than trying to piece together whether an invention is obvious after all of the work of invention has been done based on a "battle of scientific experts." *See Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1370 (Fed. Cir. 2012).

Accordingly, the objective evidence can carry the day, even where (with the aid of hindsight) an invention may seem obvious. For example, in *United States v. Adams*, the Supreme Court determined that Mr. Adams' claimed water battery was non-obvious "[d]espite the fact that each of the elements of the [claimed invention] was

well known in the prior art." 383 U.S. 39, 51 (1966). Primary among the reasons for reaching this result, the Court noted that "the Adams battery 'wholly unexpectedly' has shown 'certain valuable operating advantages over other batteries' while those from which it is claimed to have been copied were long ago discarded" and that noted experts at the time initially doubted the invention then celebrated it. *See id.* at 51–52. Similarly, this Court has found that objective indicia are particularly important where, "once the problem and solution appear together in the patent disclosure, the advance seems self-evident." *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1379 (Fed. Cir. 2012). Thus, even where "the claims contained elements that were not new," the claim could still be non-obvious based on the objective indicia. *Kinetic Concepts*, 688 F.3d at 1369–70.

Here, the district court made two structural errors regarding objective indicia evidence. First, the district court relegated them to secondary status, by reaching a conclusion that the claims were obvious before even considering the objective indicia. In this process, the district court also clearly erred in finding a lack of skepticism and praise.[6] Second, the district court discounted evidence of long-felt need and commercial success because the district court found that other objective indicia were

[6] The district court also erroneously rejected unexpected results, but based that finding primarily on its prima facie case. (Appx66.) Accordingly, we address that error primarily in Section B, below.

not proven. Before discussing these errors, though, we first explain why the objective indicia are a powerful and unbiased indication that Amarin's claims are non-obvious.

1. Objective Indicia Are Powerful Evidence in this Case and Confirm the Claims Are Not Obvious

This case is a textbook example of why objective indicia serve as an important, unbiased check against hindsight. As noted above, the district court found Amarin's claims obvious over the Lovaza® PDR in light of Mori, and, secondarily, Hayashi and Kurabayashi. (Appx57–61.) According to the district court, the Lovaza® PDR taught treating patients with severe hyperglyceridemia with a "commercially-available preparation of EPA and DHA administered at 4 grams/day," but which caused a "significant increase" in patients' LDL-C. (Appx23–24.) Also according to the district court, Mori taught that EPA effectively lowers a patient's triglycerides without raising the patient's LDL-C (albeit in a completely different population of patients, but let's just brush over that). (Appx24–25.) Obviously, a person trying to solve the problem of Lovaza® (a rise in LDL-C levels) would simply just take out the DHA (and the other constituents in Lovaza®) and use pure EPA.

This theory, though, falls completely apart when the objective indicia are considered. For example—if (as the district court found) it was so obvious that pure EPA would be an effective treatment for severe hyperglyceridemia without raising LDL-C, why did no one else undertake this solution before Amarin? The problem of LDL-C increases in treating severe hypertriglyceridemia had been recognized since the

1970s, and pure EPA products had been on the market in Japan for over fifteen years. (Appx88327; Appx4151–4152 at 40:24-41:15 (Manku); Appx1488–1489 (Heinecke).) Mori itself dates from 2000—almost a decade before Dr. Manku conceived his invention. (Appx88480.) And Mori's purported key finding—that EPA is effective to treat patients with less severe forms of hypertriglyceridemia without raising LDL-C levels—is no different than those in other studies from even earlier, including Hayashi from 1995. Yet, despite all of this information being available, no one before Dr. Manku thought to use this supposedly obvious way to treat severely hypertriglyceridemic patients. *See Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1355 (Fed. Cir. 2013) (rejecting obviousness finding where "Turi was publicly available in the prior art for twenty-two years before the '013 patent was filed, yet there is no evidence that anyone sought to improve Turi with vitamin D").

Indeed, the obviousness story here appears to go backwards. Mori not only significantly pre-dates Dr. Manku's invention, it also significantly pre-dates Lovaza®, first approved in the United States in 2004. (*Compare* Appx88408–88409 *with* Appx88480.) Normally, one would think that if Mori so clearly taught that using EPA was an effective treatment for severe hypertriglyceridemia that, unlike all previous treatments, didn't raise LDL-C, the makers of Lovaza® or some other drug developer would surely have turned to at least study pure EPA as a treatment for severe hypertriglyceridemia. After all, based on the opinion's reasoning, the prior art already had made it "obvious" for years that pure EPA would not raise LDL-C in severe

hypertriglyceridemia patients, while DHA would. But nobody did. They instead chose to use a mixture of predominantly EPA and DHA, which resulted in the typical rise in LDL-C. (Appx44323–44324.) Defendants' theory, adopted by the district court, makes no logical sense.

All of this is evidence of a long-felt, but unmet need. Dating back to the 1970s, there was a need for a treatment that could reduce severe hypertriglyceridemic patients' triglycerides without concomitantly raising their cardiovascular risk by substantially increasing LDL-C. (Appx2329–2332 at 1575:2-1578:11; Appx2466–2471 at 1712:6–1717:2 (Toth).) The previous answer to this problem—prescribing a statin—was inadequate, as any additional drug raises the possibility of new side effects, because patients are far less likely to take two pills rather than just one, and because most patients simply stopped taking statins. (Appx1412–13 at 813:8–814:2 (Heinecke).) And, for some patients—specifically patients who can't tolerate statins—this "solution" was no solution at all. (Appx2352–2353 (Toth).)

And while the district court understood that Dr. Manku's invention solved this long-felt need, it failed to give proper weight to this finding because it had already found the invention obvious. As this court has explained, "[e]vidence of a long-felt but unresolved need can weigh in favor of the non-obviousness of an invention because it is reasonable to infer the need would not have persisted had the solution been obvious." *Apple*, 839 F.3d at 1056. Yet instead of asking how its finding that the inventors solved a long-felt need affected the overall obviousness analysis, the

district court dismissed it almost out of hand, remarkably stating that though the "Asserted Claims represent an improvement"—that improvement was "a *prima facie* obvious one." (Appx67.) This stands the objective consideration of long-felt need on its head, by giving it ***less*** weight because a district court has already found an invention *prima facie* obvious.

The district court also failed to ask or answer ***why*** this long-felt need persisted for so long. The answer, as Amarin demonstrated at trial, is that skilled artisans would have believed that pure EPA would have the same effect on patients with severe hypertriglyceridemia that the other approved treatments before VASCEPA® had—a "surge" in LDL-C. (*See supra* Fact Section I.B.3.) As he testified, Dr. Manku had "great difficulty in convincing" his colleagues at Amarin and those outside the company as to "why ethyl-EPA would be effective in lower[ing] triglycerides significantly in very high patient population, with those over 500 [mg/dL], and would not affect other lipid parameters." (Appx4193 at 82:9–18.)

Again, while the district court recognized that Dr. Manku faced skepticism in fact, because it had already concluded the invention was obvious, it was unwilling to give this powerful evidence any real weight. The Court cited internal meeting notes from a panel of experts hired by Amarin who predicted before the MARINE trial that "LDL-C is likely to go up as it does with virtually all tg lowering therapies in this group of patients." (Appx68; *see also* Appx47720.) Yet, because the district court had already formed an opinion on obviousness, it worked hard to minimize the

importance of this evidence, rejecting it because the experts' view "does not appear to account for Mori." (Appx68.) In other words, the experts' skepticism was not entitled to weight because the district court had already decided it was wrong—i.e., that Mori taught that LDL-C would not go up in patients with severe hypertriglyceridemia, even though Mori relates to a different patient population, those with only mildly elevated triglycerides. The district court never considered whether the experts' skepticism might indicate that it was the ***district court's*** reading of Mori that was wrong.

This is what the objective indicia, when properly considered, are intended to do—to serve as a check on hindsight by preventing the court from "read[ing] into the prior art the teachings of the invention in issue." *Apple*, 839 F. 3d at 1052. Indeed, ***all*** skepticism of a proven invention appears incorrect in hindsight, which is why it is the fact of contemporaneous skepticism, and not an after-the-fact judgment of its wisdom, that is properly weighed against obviousness. "Expressions of disbelief by experts constitute strong evidence of nonobviousness." *Envtl. Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693, 697–98 (Fed. Cir. 1983) (citing *Adams*, 383 U.S. at 52).

Moreover, to the extent the district court found that the experts were not aware of Mori's results, this finding is both implausible and clearly wrong. It is implausible because the notes refer to "***this*** group of patients," i.e., the population of severe hypertriglyceridemic patients, not those with mild dyslipidemia as in Mori. And it is clearly wrong because the participants did know about Mori. An additional set of

contemporaneous notes refers to Mori (Appx91278–91284 at Appx91282), as does the invitation packet to the meeting (Appx43970; Appx43986; Appx43992; Appx44015–44019). Indeed, the invitation packet explicitly provided Mori's EPA results, as well as other prior art studies that tested EPA in patients without severe hypertriglyceridemia. (Appx43986; Appx43995; Appx44015–44020.)

Similarly, the district court also failed to give fair consideration to evidence as to how Amarin's patented treatment methods were "viewed in the marketplace, by those directly interested in the product." *See Kinetic Concepts*, 688 F.3d at 1370. As one would expect when a company solves a long-felt but unmet need, VASCEPA® received significant recognition. One prominent doctor recognized that VASCEPA® was a "real advance in the treatment of triglycerides" because "[i]t gives you all the benefits without the downside" and that Amarin's invention proved that "small companies [can still] do innovative things." (Appx86650; *see also* Appx48698–48706 at 48702.) Instead of considering what effect this contemporaneous praise had in an obviousness analysis, the district court was quick to write it off, erroneously characterizing the praise as "equivocal" because doctors initially expressed "caveats" about the early results of VASCEPA® because they had not yet been peer-reviewed. (Appx68; Appx42; *see also* Appx88649.) The court apparently did not consider the possibility that doctors were understandably wary of these surprising results because they were inconsistent with their prior understanding of the disease, and that their

hesitance to accept the surprising results was more likely simply further evidence of the skepticism Amarin's inventors faced in pursuing their inventions.

As to VASCEPA®'s unexpected lowering of Apo-B, the district court erred in brushing this aside based on Kurabayashi. While we address below in Section B the district court's error in relying on Kurabayashi as part of its prima facie case, the district court's only other basis for rejecting this unexpected result was its statement that the examiner, who cited Apo-B lowering as an unexpected result in allowing the claims, was not aware of Kurabayashi. (Appx62.) This is wrong, as Kurabayashi was before the examiner during prosecution and listed on the face of the patents-in-suit. (Appx79.)

Finally, as one would also expect when a company comes out with a much-needed new method of treating a life-threatening condition, VASCEPA® has enjoyed success in the marketplace. (Appx39–42.) As this Court has held, commercial success due to the merits of a patented invention is powerful evidence of non-obviousness. *See, e.g.*, *Leo Pharm.*, 726 F.3d at 1358; *Al-Site Corp. v. VSI Int'l, Inc.*, 174 F.3d 1308, 1325 (Fed. Cir. 1999). Yet again, the district court failed even to ask why, if this invention were so obvious, other, larger and much more well-funded companies than Amarin didn't seize upon the commercial opportunity. Instead, because it had already reached its conclusion, the district court perfunctorily stated in one line that commercial success "weighs in favor" of non-obviousness, without anything more. (Appx69.)

2. The District Court Legally Erred by Concluding Obviousness Before Considering Objective Indicia

Fundamentally, the district court arrived at the wrong answer because it asked the wrong question. The question the district court should have asked was whether the claims would have been obvious based on consideration of "***all*** evidence of obviousness and non-obviousness"—including evidence of objective indicia. *Cyclobenzaprine*, 676 F.3d at 1077 (emphasis in original). This is because objective indicia are not second-class citizens in the obviousness analysis—they "may often be the most probative and cogent evidence in the record." *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983); *see also Ortho-McNeil*, 520 F.3d at 1365. As such, "[a]ll evidence" including objective indicia evidence "must be considered *before* a conclusion on obviousness is reached." *Lindemann Maschinenfabrik GMBH v. Am. Hoist & Derrick Co.*, 730 F.2d 1452, 1461 (Fed. Cir. 1984) (emphasis in original).

This is not the question the district court answered. Instead of looking to ***all*** of the evidence before reaching a determination of obviousness, the district court first considered only an erroneous "prima facie" case of obviousness—namely the content of the prior art, the scope of the prior art, and the motivations and expectations of a skilled artisan. (*See* Appx57–61.) Based on the court's consideration of the "prima facie" obviousness case, but ***before*** considering any evidence of objective indicia, the Court determined that "defendants presented clear and convincing evidence at Trial that all Asserted Claims are invalid as obvious." (Appx57.) Then and only then did

the district court look to the objective indicia evidence, improperly shifting the burden of persuasion to Amarin, and asking whether the objective indicia evidence "overc[a]me the Court's finding that all Asserted claims are prima facie obvious." (Appx69.) *See ZUP, LLC v. Nash Mfg., Inc.*, 896 F.3d 1365, 1373 (Fed. Cir. 2018) ("Our precedent is clear that the burden of persuasion remains with the challenger during litigation because every issued patent is entitled to a presumption of validity" even though "a patentee bears the burden of production with respect to evidence of secondary considerations").

To be sure, the district court paid lip service to this Court's precedents regarding secondary considerations—stating that they must be considered. (*See* Appx61.) But this Court's precedents explain that what matters is not only that evidence of objective indicia must be considered but ***how*** that evidence is considered. For example, in *Lindemann Maschinenfabrik*, this court found "error" where a district court first reached a "conclu[sion] that the claimed invention would have been obvious from the prior art" and then looked "only to see whether" the proffered evidence of objective indicia "was so overwhelming as to overcome that conclusion." 730 F.2d at 1461. And in *Cyclobenzaprine*, the Court found that "[t]he district court erred, however, by making its finding that the patents in suit were obvious before it considered the objective considerations." 676 F.3d at 1075; *see also Apple*, 839 F.3d at 1048 ("A determination of whether a patent claim is invalid as obvious under § 103 requires consideration of all four *Graham* factors, and it is error to reach a conclusion

of obviousness until all those factors are considered."). This is exactly the erroneous approach taken by the district court here. Instead of treating the objective indicia evidence as part of the core obviousness analysis, the district court relegated them to being a mere "afterthought." *Leo Pharm.*, 726 F.3d at 1358.

Amarin's complaint here is not just semantics. The powerful objective indicia evidence here lays Defendants' obviousness theory bare—revealing that under the clothes of what appears to be a simple-sounding obviousness theory lies nothing but hindsight. Yet, at each turn, the district court either discounted or minimized the objective indicia evidence because it had already reached a conclusion of obviousness. The result was a series of findings inconsistent with the record and each other. The district court found that VASCEPA® satisfied a long-felt but unmet need and was a commercial success, yet somehow received only "equivocal" praise. And experts' contemporaneous skepticism was rejected on the thinnest of reeds, in the face of evidence that should have caused the district court to give that skepticism more weight, not less.

None of this is to say that a district court commits error whenever it utters the words "prima facie case" in conducting an obviousness analysis. As this Court recognized in *Cyclobenzaprine*, this Court's precedents contain decisions using this terminology. *See* 676 F.3d at 1077. However, none of these cases sanction reaching a conclusion of obviousness before considering the objective indicia—"even panels that have used the 'prima facie' and 'rebuttal' language generally have made clear that a fact

finder must consider *all* evidence of obviousness and nonobviousness before reaching a determination." *Id.* But, ultimately, what matters is not the language the court uses but the mode of analysis, which here violated this Court's precedents requiring that all evidence actually be considered before a court decides obviousness.

3. The District Court Improperly Required Plaintiffs to Show Every Objective Indicia Raised Supported Non-Obviousness

In addition to improperly pitting objective indicia against a "prima facie" case of obviousness, the district court also legally erred by pitting the categories of objective indicia against each other. Specifically, the Court held that the objective indicia it found present were "outweighed by the fact that the Court found" other categories of objective indicia not present. (Appx69.) The district court did not cite any caselaw supporting this approach, because there is none.

To the contrary, this Court has specifically held that a lack of objective indicia "does not weigh in favor of obviousness." *Miles Labs, Inc. v. Shandon Inc.*, 997 F.2d 870, 878 (Fed. Cir. 1993) (citing *Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955 (Fed. Cir. 1986)). Nor is there any reason why one of the objective indicia, such as commercial success, should be "outweighed" by the purported failure to prove another, such as praise. Following the district court's logic, Amarin would have been better off had it simply brought less evidence, because then there would have been fewer categories of objective indicia to count against those that the district court found. This cannot be the law.

This Court has repeatedly found that evidence regarding only a few objective indicia can still be strong evidence showing non-obviousness. *See, e.g.*, *Cyclobenzaprine*, 676 F.3d at 1080–84 (long-felt need and failure by others supported a conclusion of non-obviousness); *Millennium Pharm., Inc. v. Sandoz, Inc.*, 862 F.3d 1356, 1368–69 (Fed. Cir. 2017) (unexpected results and long-felt need supported a conclusion of non-obviousness); *Institut Pasteur v. Focarino*, 738 F.3d 1337, 1346–48 (evidence of competitors licensing and industry praise warranted reversal of PTAB's conclusion of obviousness). Thus, even if the district court were correct that only two objective indicia favored plaintiffs—and it was not—there was no reason to devalue those two categories because Amarin did not succeed in proving other, unrelated objective indicia. This additional legal error further minimized the weight that the district court gave to objective indicia, and further warrants reversal.

B. Hindsight Bias Infected the Court's Motivation and Reasonable Expectation Analysis

"[T]he best defense against hindsight-based obviousness analysis is the rigorous application of the requirement for a showing of a teaching or motivation to combine the prior art references." *Ecolochem, Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1371 (Fed. Cir. 2000). Linked to motivation is reasonable expectation of success, which also must be rigorously applied to avoid hindsight. *See, e.g.*, *OSI Pharm., LLC v. Apotex Inc.*, 939 F.3d 1375, 1385 (Fed. Cir. 2019) (rejecting obviousness finding in part because

"[i]t is only with the benefit of hindsight that a person of skill in the art would have had a reasonable expectation of success in view of the asserted references").

The district court's analysis of both these concepts was anything but "rigorous." To prevail, Defendants had to show by ***clear and convincing evidence*** that a skilled artisan would have been motivated to modify the prior Lovaza® treatment to arrive at the claimed EPA-only regimen, and that she would have reasonably expected that doing so would not, like all the other approved treatments, dramatically raise LDL-C. The problem for Defendants, and the district court, is that there is nowhere near enough evidence in the record to meet that high burden, and the district court legally erred in concluding otherwise. Indeed, the only way the district court reached its conclusion was through legal and factual error that ignored the critical teachings in the art about the differential LDL-C effects of triglyceride-lowering agents in patients with and without severe hypertriglyceridemia, and which effectively required Amarin to prove its invention non-obvious, as opposed to Defendants proving the opposite. These errors require reversal.

1. The District Court Erred in Ignoring Defendants' Lack of Evidence on the Key Issue—the Effect of EPA-Only Treatments on LDL-C in Severe Hypertriglyceridemia Patients

Fundamentally, the court legally erred in concluding a skilled artisan would have found it obvious to change Lovaza®'s omega-3 mixture including DHA and EPA meant for one patient population—those with ***severe hypertriglyceridemia***—

based on references showing the use of pure EPA in a fundamentally different population—those with ***mild to moderately elevated triglycerides***, i.e., Mori, Hayashi, and Kurabayashi. This difference in patient populations is critical, because, as the record evidence made clear, skilled artisans understood patients with severe hypertriglyceridemia responded differently to triglyceride-lowering drugs because of their genetics than those with milder hypertriglyceridemia. (*See supra* Fact Section I.B.2; Appx47–48.) As the district court found, and the experts agreed, all prior art treatments for severe hypertriglyceridemia "***dramatically increase[d]*** LDL-C levels[.]" (Appx5; *see also* Appx2329–2333 (Toth); Appx2336-2344 (Toth); Appx43939–43940; Appx44323–44324; Appx887–890 (Budoff); Appx953 (Budoff); Appx1450–1451 (Heinecke); Appx1430–1431 (Heinecke); Appx47720.) Yet in patients with milder forms of hypertriglyceridemia, these same treatments actually ***lowered*** LDL-C levels or raised them only slightly, if at all. (*See supra* Fact Section I.B.3; Appx1474–1478 (Heinecke).)

In its opinion, the district court regrettably ignored this important difference between the patient populations that extensive record evidence demonstrates. (*See supra* Fact Sections I.B.3, III.) Because of this, the court's analysis did not grapple with the fundamental problem at the heart of Defendants' case: that Mori and the rest of the prior art taught ***nothing*** about LDL-C effects in severe hypertriglyceridemia patients. As Dr. Heinecke admitted, before Amarin's invention, ***no one knew*** how EPA alone would work in severe hypertriglyceridemia patients:

> I don't think there's ***any evidence*** in the prior literature about what the impact of EPA would be on LDL cholesterol in patients with triglycerides above 500 milligrams per deciliter.

(Appx1398–1399 at 800:2–5; *see also id.* at 799:9–11 ("I'm not arguing here that we know what the impact is of EPA on LDL cholesterol levels above 500 milligrams per deciliter.").)

Without such a teaching, Defendants did not show that a skilled artisan would have had reason to modify Lovaza® to create a pure EPA treatment based on the prior art, or that she would have had a reasonable expectation that pure EPA would somehow behave differently than every other approved treatment for severe hypertriglyceridemia. *See Millennium Pharm.*, 862 F.3d at 1365–66 (motivation to combine erroneous where "no reference suggest[ed]" making the claimed modification to improve stability and "undisputed facts" were to the contrary); *Cyclobenzaprine*, 676 F.3d at 1070 ("While it may have been obvious to experiment with the use of the same PK profile when contemplating an extended-release formulation, there is nothing to indicate that a skilled artisan would have had a reasonable expectation that such an experiment would succeed in being therapeutically effective.").

The district court's finding otherwise begins with a hindsight-based premise and ends with a faulty conclusion: that "a skilled artisan would have wanted to know which active ingredient in Lovaza—EPA or DHA—was responsible for the LDL-C increase (if not both), and that Mori addressed this exact issue." (Appx57.) But

Defendants never showed that a skilled artisan, looking at Lovaza®'s LDL-C effects, would have assumed that either EPA or DHA (or both) were the cause of the LDL-C increase or that removing one of them would in any way help. Instead, the evidence showed that skilled artisans believed that LDL-C increases resulted from the increased conversion of VLDL to LDL—in other words, that they were an unfortunate but inevitable result of all approved triglyceride-lowering drugs in this patient population. (Appx107777–107783; Appx47720; Appx2344–2352 (Toth); Appx2460 (Toth); Appx48848; Appx44256–44258; Appx48910–48911; Appx43935–43936.)[7]

In this regard, Dr. Heinecke never presented the district court with any alternative mechanism for the known differential LDL-C effects that was accepted in the art. Instead, he "imagined" different mechanisms. (Appx1457–1458.) And as for the prior art that discussed the accepted mechanism, his basis for criticizing it was to quibble with the verbiage of prior art articles like McKenney (Appx1471) and obstinately disagree with statements from the FDA on, for example, the label of Tricor®. (Appx43935–43936; Appx1480–1482 (Heinecke); *see also* Appx43686; Appx1462–1463 (Heinecke).) Such unsupported expert testimony does not provide clear and convincing evidence of obviousness. *See ActiveVideo Networks, Inc. v. Verizon*

[7] Indeed, the Carlson reference called this a "general phenomenon" as far back as 1977. (Appx107779.) Without any citation, the district court rejected Carlson as not reflecting what a skilled artisan would believe in 2008 because it was from 1977. (Appx60.) Given that all experts and the district court agreed that niacin, and all other approved treatments for severe hypertriglyceridemia before the invention, raised LDL-C, this was clear error.

Commc'ns, Inc., 694 F.3d 1312, 1327 (Fed. Cir. 2012); *Innogenetics N.V. v. Abbott Labs.*, 512 F.3d 1363, 1373 (Fed. Cir. 2008).

The district court's citation of Dr. Toth's agreement that "a skilled artisan seeing that there's DHA and EPA in Lovaza, and seeing a side effect, would at least consider whether the side effect could be associated with only DHA or only EPA" also provides no support to Defendants' case. (Appx57; Appx2580–2583 at 1787:6–10 (Toth).) Notably, the district court's excerpt omits Dr. Toth's response to the preceding question. When first asked whether it would have been obvious to consider whether Lovaza's LDL-C effects were due to only one of Lovaza®'s constituents, Dr. Toth answered "[n]ot in patients with severe hypertriglyceridemia." (Appx2580–2581 at 1786:23–1787:2.) This is in line with Dr. Toth's extensive testimony that ordinary artisans understood that it was not the specific treatments that caused the LDL-C increases, but rather the condition itself. (*See* Appx2344–2352.)

Even crediting the district court's parsing of Dr. Toth's testimony, however, it shows only that a skilled artisan may have had reason to investigate the extent by which DHA and EPA might increase LDL-C in the severely hypertriglyceridemic population. But a reason to investigate is not enough to provide either the motivation to remove entirely all of the constituents of Lovaza® save one, or the reasonable expectation that doing so would prevent LDL-C increases, ***particularly where the prior art was conceded not to address what would happen if such an investigation was undertaken***. *See Sanofi Synthelabo v. Apotex, Inc.*, 550 F.3d 1075,

1088 (Fed. Cir. 2008) (rejecting obviousness of selection of one of two enantiomers as based on "hindsight knowledge" of the "desirable properties" of the chosen enantiomer); *Leo Pharm.*, 726 F.3d at 1356 (finding the claimed invention would not be "obvious to try" simply because a skilled artisan "would have been capable of selecting the correct formulation from available alternatives").

Second, the district court erred in concluding that the EPA-only references Mori, Hayashi, and Kurabayashi filled this gap, when it was undisputed that none of these references were directed to the relevant patient population, i.e., severe hypertriglyceridemia. (Appx24–30; Appx57–60.) On Mori, Dr. Heinecke admitted that the patients tested did not have "even high triglycerides, let alone very high triglycerides[.]" (Appx1495.) On Kurabayashi, he admitted that the "upper limit on triglycerides" was 400 mg/dL, and that the patients did not have severe hypertriglyceridemia. (Appx1495–1497.) And on Hayashi, Dr. Heinecke admitted that, even if there may have been 1 or 2 patients with levels above 500, "they were not measuring LDL-C values for patients over 500" and "Hayashi is ***not telling us anything*** about the effect of EPA on LDL-C values in severely hypertriglyceridemic patients[.]" (Appx1492–1494.) The district court's finding that "Mori, Hayashi, and Kurabaysahi disclosed that EPA did not increase LDL-C" (Appx58) is, at best, incomplete, in light of these admissions. For the same reason, the court's finding that Kurabayashi taught that EPA reduced Apo-B levels (Appx58; Appx66) is flawed because Kurabayashi was in the wrong population of patients—patients with ***normal***

average triglycerides (around 135 mg/dL)—not patients with severe hypertriglyceridemia. (Appx88401–88403.)

The district court also erroneously rejected Dr. Toth's testimony that "all [prior art] treatments increased LDL-C in patients with very high triglycerides," concluding "that cannot be correct, because Mori taught that EPA did not increase LDL-C levels like DHA did." (Appx59.) But, the district court itself recognized that, before Dr. Manku's invention, prior art "treatments for severe hypertriglyceridemia ***dramatically increase[d]*** LDL-C levels[.]" (Appx5.) And, again, it never explained why Mori (or any of the other EPA-only references) are even applicable to ***severe hypertriglyceridemia patients***—patients who, as discussed above, were understood to respond differently to triglyceride-lowering drugs because of their genetics. Without a link to those severe hypertriglyceridemia patients, there can be no obviousness. *See Orexo AB v. Actavis Elizabeth LLC*, 903 F.3d 1265, 1272–73 (Fed. Cir. 2018) (reversing obviousness determination where defendant conceded that no prior art taught claimed use of citric acid and failed to present "clear and convincing evidence of a teaching or suggestion to use citric acid particles as a carrier . . . or that the actual beneficial results would be obtained").

The primary rationale for the district court's application of Mori-type prior art to severe hypertriglyceridemia patients appears to have been its finding that Amarin's argument that those patients respond differently to triglyceride-lowering drugs than non-severe hypertriglyceridemia patients "lack[ed] evidentiary support[.]" (Appx60.)

Yet all the court relied on for this conclusion was Dr. Toth's unremarkable testimony that drugs that lower triglycerides in the non-severe patient population also lower triglycerides in the severe patient population. (Appx60.) Amarin never disputed this, and it is irrelevant to the critical question, on which Defendants bore the burden of proof: whether triglyceride-lowering drugs cause different effects ***on LDL-C*** in the different patient populations. And on that question, as explained above, the overwhelming evidence showed a distinct difference—one which would have ***dissuaded*** a skilled artisan from relying on Mori to modify Lovaza®'s treatment for severe hypertriglyceridemia patients. The district erred by ignoring this key evidence. *See Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1579–80 (Fed. Cir. 1987) (rejecting the district court's factual findings as clearly erroneous where the court relied on hindsight and failed to reconcile differences between the prior art and the claimed invention); *Cyclobenzaprine*, 676 F.3d at 1073–75.

Amarin's internal documents, on which Defendants heavily relied at trial and the district court credited—say nothing different. (*See* Appx31; Appx675–715 (Ketchum); Appx719–726 (Ketchum); Appx90245–90269; Appx90286–90296; Appx90297–90417; Appx90418-90431.) That these documents characterized some of the prior art, including Mori, as showing that EPA was "LDL-neutral," does not change the critical and undisputed fact that Mori is only concerned with patients with mildly elevated triglycerides, not severe hypertriglyceridemia as required by the claims, which the documents note. (*See e.g.*, Appx90257 (noting Mori concerned baseline

triglycerides of less than 200 mg/dL); Appx90364–90365 (noting Mori concerned baseline triglycerides of less than 200 mg/dL and that none of the studies assessing EPA "recruited patients with severe hypertriglyceridemia"); Appx90428; *see also* Appx90288–90289.)

Nor do these documents show that Amarin's inventors, who had access to a wealth of additional clinical information on EPA on which to base their insights, merely did what the prior art taught, as Defendants claimed. "[T]he path that leads an inventor to the invention is expressly made irrelevant to patentability by statute." *Life Techs., Inc. v. Clontech Labs., Inc.*, 224 F.3d 1320, 1325 (Fed. Cir. 2000); 35 U.S.C. § 103(a) (2011); *see also Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012) ("The inventor's own path itself never leads to a conclusion of obviousness; that is hindsight."). That the inventors unsurprisingly were aware of Mori as just one of many "bits and pieces" to the puzzle cannot show, by clear and convincing evidence, that a skilled artisan would have found it obvious to modify Lovaza® based on Mori. As noted above, experts provided with information about Mori's results at the relevant time still believed that EPA would raise LDL-C in severe hypertriglyceridemia patients. (Appx47720; *see supra* Fact Section I.B.1.)

Finally, the district court's citation of the examiner's initial finding of obviousness that the applicants later overcame was also legal error. (Appx59; Appx57815–57822.) Almost every patent ever allowed was once rejected by an examiner. That the examiner initially found a prima facie case to use EPA to lower

triglycerides in severe hypertriglyceridemia patients during prosecution does not provide any evidence, let alone clear and convincing evidence, to show obviousness after the patent has issued, and is presumed valid. *See* 35 U.S.C. § 282; *Quad Envtl. Techs. Corp. v. Unions Sanitary Dist.*, 946 F.2d 870, 876 (Fed. Cir. 1991) (emphasizing that obviousness determinations are made by the courts "without deference to the rulings of the patent examiner").

2. The District Court Improperly Shifted the Burden to Amarin to Prove Non-Obviousness and then Erred in Ignoring the Evidence Amarin Presented

Without clear and convincing evidence in the record, the only way the Court reached its obviousness conclusion was by shifting the burden to Amarin to show non-obviousness. Instead of requiring Defendants to show that a skilled artisan would have reasonably expected Mori's findings to be applicable to severe hypertriglyceridemia patients, the district court improperly required ***Amarin*** to show the opposite:

> There was ***no reason to expect*** differently for LDL-C. ***Dr. Toth cited no evidence*** that the 500 mg/dL threshold reflects any difference in how patients metabolize drugs, or any relationship between that specific threshold and LDL-C.

(Appx60.) This is legally improper and contrary to the burden of proof on invalidity, which always rests with the challenger. *See, e.g.*, *Circuit Check Inc. v. QXQ Inc.*, 795 F.3d 1331, 1337 (Fed. Cir. 2015) (finding error where district court "concluded that these

claims were obvious because [the patentee] did not explain why the additional limitations rendered the claims non-obvious").

The court's conclusion also constituted factual error because it was directly contradicted by the trial record.[8] Dr. Toth cited ***extensive evidence*** that patients with triglycerides of at least 500 mg/dL experience an increase in LDL-C with triglyceride-lowering drugs because of genetic predispositions not shared by patients with triglycerides under 500 mg/dL. (*See supra* Fact Section I.B.2; Appx2325–2326 (Toth); Appx2329–2332 (Toth); Appx2336-2344 (Toth); Appx43939–43940; Appx44323–44324.) It is irrelevant that Dr. Toth stated the 500 mg/dL level "***was not set***" because of this differential LDL-C effect. (Appx60.) It does not matter ***why*** the 500 mg/dL demarcation was set; what matters is the known effects on LDL-C for patients with triglycerides at or above that level. And Dr. Toth's testimony was clear that "[t]he 500 threshold does, in fact, identify another group of patients who responds ***very differently*** to triglyceride-lowering medications in terms of their LDL increases." (Appx2653-2654 at 1859:22-1860:2.)

Similarly, the district court's reliance on Dr. Heinecke's testimony is, charitably, incomplete. *See Cyclobenzaprine*, 676 F.3d at 1073–74 (finding error where district court

[8] As noted above, the district court copied this entire passage from Defendants' proposed findings. Given its conclusory nature, the Court should have great concern about the weight given to these findings. *See, e.g. U.S. v. El Paso Nat. Gas Co.,* 376 U.S. 651, 656 (1964) (findings "drawn with the insight of a disinterested mind are, however, more helpful to the appellate court.").

relied on one portion of a witness's testimony but ignored other portions). Immediately after saying there is no "magical mechanistic difference" between triglyceride levels of 400, 500, and 600 mg/dL, which was cited by the district court, Dr. Heinecke admitted:

> The concern with pancreatitis is when one actually gets up above the 1000-milligram per deciliter, and this was something that was not well understood back in 2008. We knew that ***somewhere above 500 milligrams per deciliter the system for clearing triglycerides jams up. But no one knew what that level was***, but, we knew it was above 500 milligrams per deciliter."

(Appx1395–1396 at 796:17–797:2.) Dr. Heinecke's testimony is thus consistent with Dr. Toth's—before Amarin's invention, a skilled artisan would have understood that patients with triglyceride levels above 500 mg/dL ***do*** metabolize triglyceride-lowering drugs differently than those with levels below 500 mg/dL.

Likewise, Dr. Heinecke's general statement that "[q]ualitatively, [the effects of medications] tend to be the same" regardless of baseline triglyceride levels, which the district court credited, is insufficient to show that an ordinary artisan would understand that the ***LDL-C effects*** would be the same. (Appx1396 at 797:16–18.) This is particularly so given that, as the evidence elided by the district court shows, the very problem with severe hypertriglyceridemia was that the LDL-C effects were known ***not*** to be the same in patients who have very high baseline triglycerides compared to others. (Appx60–61; Appx1396 (Heinecke); *see, e.g.*, Appx1475–1478 (Heinecke).) Indeed, this was why there was a long-felt need. The district court's

apparent conclusion that baseline triglyceride levels do not matter in relation to LDL-C levels has no actual support in the record.

Finally, to the extent the district court's decision is based on its determination that Hayashi included "at least one patient with triglyceride levels > 500 mg/dL" and "does not limit its conclusion regarding EPA's effects on LDL-C levels to patients with lower triglyceride levels," this is also error. (Appx26–28.) Dr. Heinecke admitted that "they were not measuring LDL-C values" for any patient above 500 and that "Hayashi is ***not telling us anything*** about the effect of EPA on LDL-C values in severely hypertriglyceridemic patients[.]" (Appx1492–1494.) There is thus no evidence or data to expand Hayashi's teachings to patients with severe hypertriglyceridemia. The court's finding that the teachings were "not limited" to patients with lower triglycerides is yet another example of legally improper burden shifting and is also clearly erroneous.

At bottom, the court's obviousness determination requires skilled artisans to throw out what they knew about approved treatments for severe hypertriglyceridemia and conclude that, based on studies in patients ***without*** that condition, EPA was likely to behave differently than every other approved treatment for the disease. But a person of ordinary skill is "presumed to be one who thinks along the line of conventional wisdom in the art," *Standard Oil Co. v. American Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985), not one who ignores the teachings of that art to reach different conclusions. The district court's obviousness judgment substitutes its

hindsight views of the prior art for the ordinary artisan's. That judgment should be reversed.

CONCLUSION

For the reasons above, the Court should reverse the district court's finding that the asserted claims are obvious.

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Amarin Pharma, Inc. and Amarin Pharmaceuticals Ireland Limited

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.

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/s/ Jonathan E. Singer
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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 13,984 words as determined by Microsoft Word.

Dated: May 12, 2020

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