No. 2020-1723

United States Court of Appeals for the Federal Circuit

AMARIN PHARMA, INC., AMARIN PHARMACEUTICALS IRELAND LIMITED,
PLAINTIFFS-APPELLANTS

v.

HIKMA PHARMACEUTICALS USA INC., HIKMA PHARMACEUTICALS INTERNATIONAL LIMITED, DR. REDDY'S LABORATORIES, INC., DR. REDDY'S LABORATORIES, LTD.,
DEFENDANTS-APPELLEES

APPEAL FROM THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF NEVADA, CASE NO. 2:16-CV-02525-MMD-NJK, CHIEF JUDGE MIRANDA M. DU

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June 16, 2020

CERTIFICATE OF INTEREST

Counsel for Defendants-Appellees Hikma Pharmaceuticals USA Inc. and Hikma Pharmaceuticals International Limited certifies the following:

1. Full names of parties represented by me:

Hikma Pharmaceuticals USA Inc.
Hikma Pharmaceuticals International Limited

2. Name of real party in interest (Please only include any real party in interest NOT identified in Question 3) represented by me is:

N/A

3. Parent corporations and publicly held companies that own 10% or more of stock in the parties:

Hikma Pharmaceuticals USA, Inc. is an indirect wholly-owned subsidiary of Hikma Pharmaceuticals PLC. Hikma Pharmaceuticals PLC is publicly listed. No other publicly held companies own 10% or more of the stock of Hikma Pharmaceuticals USA, Inc.

Hikma Pharmaceuticals International Limited is an indirect wholly-owned subsidiary of Hikma Pharmaceuticals PLC. Hikma Pharmaceuticals PLC is publicly listed. No other publicly held companies own 10% or more of the stock of Hikma Pharmaceuticals International Limited.

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:

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5. The title and number of any case known to counsel to be pending in this or any other court or agency that will directly 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.,
No. 2:18- cv-01596-MMD-NJK (D. Nev.)

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2. Name of real party in interest (Please only include any real party in interest NOT identified in Question 3) represented by me is:

N/A

3. Parent corporations and publicly held companies that own 10% or more of stock in the parties:

Dr. Reddy's Laboratories, Inc. is a wholly owned subsidiary of Dr. Reddy's Laboratories, S.A., which is a wholly owned subsidiary of Dr. Reddy's Laboratories, Ltd., which is a publicly traded company. No publicly held corporation owns 10% or more of the stock of Dr. Reddy's Laboratories, Ltd.

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:

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5. The title and number of any case known to counsel to be pending in this or any other court or agency that will directly 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.,
No. 2:18- cv-01596-MMD-NJK (D. Nev.)

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TABLE OF CONTENTS

Page

TABLE OF AUTHORITIES vii

GLOSSARY OF ABBREVIATIONS xii

STATEMENT OF RELATED CASES xiii

INTRODUCTION 1

COUNTER-STATEMENT OF ISSUES 6

COUNTER-STATEMENT OF THE CASE 6

A. Lovaza, an EPA-DHA mixture, was approved to treat severe hypertriglyceridemia, but had a side effect of increasing LDL-C. 6

B. The prior art taught that EPA, unlike DHA, reduces triglycerides without increasing LDL-C, and also reduces Apo B. 8

C. Amarin relied exclusively on prior-art studies to develop Vascepa. ... 12

D. Amarin mischaracterized prior art during prosecution, but the examiner still found the claims prima-facie obvious. 17

E. Based on a battle of experts at trial, the district court found clear and convincing evidence that all asserted claims are invalid. 19

SUMMARY OF ARGUMENT 23

STANDARD OF REVIEW 26

ARGUMENT 27

I. Amarin fails to show harmful error in the district court's secondary-considerations analysis. 27

A. Amarin's attempts to manufacture legal error lack merit. 27

1. The district court did not "shift the burden"—it followed on-point precedent that Amarin fails to cite. 27

2. The district court did not use Amarin's alleged secondary considerations as affirmative evidence of obviousness—it found them unpersuasive and "weak." 30

TABLE OF CONTENTS (continued)

Page

B. Amarin's alleged legal errors would be harmless. 31

1. The claims would be obvious even if the district court had given commercial success and long-felt need greater weight. .31

2. Vascepa's alleged commercial success cannot weigh in favor of nonobviousness because it lacks a nexus to the claims. 33

C. Amarin shows no clear error in the district court's rejection of alleged secondary considerations. 35

II. Amarin fails to show clear error in the district court's factual findings on motivation to combine and reasonable expectation of success. 39

A. The record amply supports the court's finding that a skilled artisan would reasonably expect pure EPA to be LDL-neutral. 40

B. Amarin's evidence concerning the LDL-C effects of products *other* than EPA in patients with triglycerides *above* 500mg/dL is irrelevant and was properly discounted. 47

C. The district court did not "shift the burden" by rejecting Amarin's arguments and considering the prosecution history. 51

III. The record supports multiple alternative grounds for affirmance. 53

A. The seven claims that allow concurrent lipid therapy were also obvious because adding a statin was expected to achieve the claimed effects, and the remaining three claims are not infringed. 53

B. Defendants do not infringe any asserted claim because their labels do not induce doctors to administer EPA for at least 12 weeks. 60

C. Alternatively, all asserted claims lack written description. 63

CONCLUSION 65

CERTIFICATE OF SERVICE

CERTIFICATE OF COMPLIANCE

TABLE OF AUTHORITIES

Page(s)

Cases

1st Media, LLC v. Elec. Arts, Inc.,
694 F.3d 1367 (Fed. Cir. 2012) 53

Acorda Therapeutics, Inc. v. Roxane Labs., Inc.,
903 F.3d 1310 (Fed. Cir. 2018) 41, 45

Adang v. Umbeck,
2007 WL 3120323 (Fed. Cir. Oct. 25, 2007) 64

Alcon Research, Ltd. v. Apotex Inc.,
687 F.3d 1362 (Fed. Cir. 2012) 46

Alza Corp. v. Mylan Labs., Inc.,
464 F.3d 1286 (Fed. Cir. 2006) 26

Bayer Pharma AG v. Watson Labs., Inc.,
874 F.3d 1316 (Fed. Cir. 2017) 33

Bruno Indep. Living Aids, Inc. v. Acorn Mobility Servs., Ltd.,
394 F.3d 1348 (Fed. Cir. 2005) 51

BTG Int'l Ltd. v. Amneal Pharm. LLC,
923 F.3d 1063 (Fed. Cir. 2019) 36

Celgene Corp. v. Peter,
931 F.3d 1342 (Fed. Cir. 2019) 37

In re Copaxone Consol. Cases,
906 F.3d 1013 (Fed. Cir. 2018) 47

Cubist Pharm., Inc. v. Hospira, Inc.,
805 F.3d 1112 (Fed. Cir. 2015) 28

In re Cuozzo Speed Techs., LLC,
793 F.3d 1268 (Fed. Cir. 2015) 5, 7, 44, 54

TABLE OF AUTHORITIES (continued)

Page(s)

In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.,
676 F.3d 1063 (Fed. Cir. 2012) 29–30, 32

In re Depomed Patent Litig.,
2016 WL 7163647 (D.N.J. Sept. 30, 2016), *aff'd sub nom. Grunenthal*, 919 F.3d 1333 62

Gillette Co. v. Energizer Holdings, Inc.,
405 F.3d 1367 (Fed. Cir. 2005) 56

Graham v. John Deere Co. of Kansas City,
383 U.S. 1 (1966) 3, 6, 20, 22–23, 30, 33

Grunenthal GMBH v. Alkem Labs. Ltd.,
919 F.3d 1333 (Fed. Cir. 2019) 57–62

Hoffmann-La Roche Inc. v. Apotex Inc.,
748 F.3d 1326 (Fed. Cir. 2014) 21, 24, 44–46

HZNP Meds. LLC v. Actavis Labs. UT, Inc.,
940 F.3d 680 (Fed. Cir. 2019) ("*Horizon*") 57–58, 60, 62

Ignite USA, LLC v. CamelBak Prods., LLC,
709 F. App'x 1010 (Fed. Cir. 2017) 4, 52

Institut Pasteur v. Focarino,
738 F.3d 1337 (Fed. Cir. 2013) 32

Intercontinental Great Brands LLC v. Kellogg N. Am. Co.,
869 F.3d 1336 (Fed. Cir. 2017) 28, 53

Iron Grip Barbell Co. v. USA Sports, Inc.,
392 F.3d 1317 (Fed. Cir. 2004) 38

ISCO Int'l, Inc. v. Conductus, Inc.,
123 F. App'x 974 (Fed. Cir. 2005) 31

Kao Corp. v. Unilever U.S., Inc.,
441 F.3d 963 (Fed. Cir. 2006) 4, 40

TABLE OF AUTHORITIES (continued)

Page(s)

Lab. Corp. of Am. Holdings v. Chiron Corp.,
384 F.3d 1326 (Fed. Cir. 2004) 50

MEHL/Biophile Int'l Corp. v. Milgraum,
192 F.3d 1362 (Fed. Cir. 1999) 26

Merck & Co. v. Teva Pharm. USA, Inc.,
395 F.3d 1364 (Fed. Cir. 2005) 45–46

Merck Sharp & Dohme Corp. v. Hospira, Inc.,
874 F.3d 724 (Fed. Cir. 2017) 4, 33

Millennium Pharm., Inc. v. Sandoz Inc.,
862 F.3d 1356 (Fed. Cir. 2017) 32

MRC Innovations, Inc. v. Hunter Mfg., LLP,
747 F.3d 1326 (Fed. Cir. 2014) 35

Munoz v. Strahm Farms, Inc.,
69 F.3d 501 (Fed. Cir. 1995) 26

Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.,
719 F.3d 1346 (Fed. Cir. 2013) 2, 23, 28–29, 51

Nuvo Pharmaceuticals (Ireland) Designated Activity Co. v. Dr. Reddy's Labs. Inc.,
923 F.3d 1368 (Fed. Cir. 2019) 63

Optivus Tech., Inc. v. Ion Beam Applications S.A.,
469 F.3d 978 (Fed. Cir. 2006) 52

Par Pharm., Inc. v. TWI Pharm., Inc.,
773 F.3d 1186 (Fed. Cir. 2014) 37

Pentec, Inc. v. Graphic Controls Corp.,
776 F.2d 309 (Fed. Cir. 1985) 32

Perfect Web Techs., Inc. v. InfoUSA, Inc.,
587 F.3d 1324 (Fed. Cir. 2009) 37

TABLE OF AUTHORITIES (continued)

Page(s)

Persion Pharm. LLC v. Alvogen Malta Operations Ltd.,
945 F.3d 1184 (Fed. Cir. 2019) 29, 41

Pfizer, Inc. v. Apotex, Inc.,
480 F.3d 1348 (Fed. Cir. 2007) 47, 52

Sarif Biomedical LLC v. Brainlab, Inc.,
725 F. App'x 996 (Fed. Cir. 2018) 50

Senju Pharm. Co. v. Lupin Ltd.,
780 F.3d 1337 (Fed. Cir. 2015) 4, 43

Spectrum Pharm., Inc. v. Sandoz Inc.,
802 F.3d 1326 (Fed. Cir. 2015) 3, 35

Stratoflex, Inc. v. Aeroquip Corp.,
713 F.2d 1530 (Fed. Cir. 1983) 32

Syntex (U.S.A.) LLC v. Apotex, Inc.,
407 F.3d 1371 (Fed. Cir. 2005) 52

Takeda Pharm. U.S.A., Inc. v. W.-Ward Pharm. Corp.,
785 F.3d 625 (Fed. Cir. 2015) 61

Teva Pharm. USA, Inc. v. Novartis Pharm. Corp.,
482 F.3d 1330 (Fed. Cir. 2007) 29

Tokai Corp. v. Easton Enters., Inc.,
632 F.3d 1358 (Fed. Cir. 2011) 28

Tokyo Keiso Co. v. SMC Corp.,
307 F. App'x 446 (Fed. Cir. 2009) 38

TypeRight Keyboard Corp. v. Microsoft Corp.,
374 F.3d 1151 (Fed. Cir. 2004) 27

Union Carbide Corp. v. Am. Can Co.,
724 F.2d 1567 (Fed. Cir. 1984) 32, 45, 62

TABLE OF AUTHORITIES (continued)

Page(s)

Univ. of Rochester v. G.D. Searle & Co.,
358 F.3d 916 (Fed. Cir. 2004) 64

Valeant Pharm. Int'l, Inc. v. Mylan Pharm. Inc.,
955 F.3d 25 (Fed. Cir. 2020) 29

Warner-Lambert Co. v. Apotex Corp.,
316 F.3d 1348 (Fed. Cir. 2003) 61

Wavetronix LLC v. EIS Elec. Integrated Sys.,
573 F.3d 1343 (Fed. Cir. 2009) 26

Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC,
683 F.3d 1356 (Fed. Cir. 2012) 34–35

ZUP, LLC v. Nash Mfg., Inc.,
896 F.3d 1365 (Fed. Cir. 2018) 3, 31

Statutes

21 U.S.C. §355(j)(5)(F)(ii).....19–21

35 U.S.C. §103 .....2, 23, 32

35 U.S.C. §112 63

35 U.S.C. §271(b) 56

35 U.S.C. §271(c) 56–57

GLOSSARY OF ABBREVIATIONS

Amarin	Plaintiffs-Appellants Amarin Pharma, Inc. and Amarin Pharmaceuticals Ireland Limited
Defendants	Defendants-Appellees Hikma Pharmaceuticals USA Inc., Hikma Pharmaceuticals International Limited, Dr. Reddy's Laboratories, Inc. and Dr. Reddy's Laboratories, Ltd.
ANDA	abbreviated new drug application
Apo B	apolipoprotein B
Br.	brief (unless otherwise noted, Amarin's opening brief, Dkt. 32)
Budoff	Amarin's clinical infringement expert, Matthew Budoff, M.D.
CNS	central nervous system
DHA	docosahexaenoic acid
EPA	eicosapentaenoic acid, also known as icosapent, icosapent ethyl, ethyl icosapentate, or EPA-E (i.e., ethyl EPA)
FDA	U.S. Food and Drug Administration
g	gram
Heinecke	Defendants' invalidity expert, Jay Heinecke, M.D.
LDL-C	low-density lipoprotein cholesterol
mg/dL	milligrams per deciliter
Peck	Amarin's FDA labeling expert, Carl Peck, M.D.
PDR	Physicians' Desk Reference (a published compilation of drug labels)
PTO	U.S. Patent and Trademark Office
TG	triglyceride
Toth	Amarin's validity expert, Peter Toth, M.D.

STATEMENT OF RELATED CASES

No previous appeal has been taken in this action.

In *Amarin Pharma, Inc. v. Dr. Reddy's Labs., Inc.*, No. 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. Amarin filed a notice of appeal of this consent judgment on May 22, 2020.

INTRODUCTION

This appeal involves six substantively identical patents that claim the same method of treatment—administering 4g/day of pure EPA for at least 12 weeks to a patient with severe hypertriglyceridemia (i.e., triglycerides ≥500mg/dL) to reduce triglycerides. As discussed below, the district court made no reversible error in concluding that the asserted claims of these patents were obvious.

EPA, like DHA, is an omega-3 fatty acid found naturally in fish oil. The properties of EPA, including its triglyceride-lowering effects, were well known in the prior art. As Amarin admits, "there were many published clinical studies relating to treating hypertriglyceridemia with pure EPA before Amarin's [claimed] invention." Br. 13. These studies included the double-blind, placebo-controlled trial by Mori, which the district court relied on below and taught the claimed 4g/day dose of pure EPA. Appx24-25. Amarin also admits the prior art included a product called Lovaza, an EPA-DHA mixture that was FDA-approved to treat severe hypertriglyceridemia at a 4g/day dose. Br. 35. Lovaza was clinically used at this dosage for more than 12 weeks. Appx23. Thus, the dispute at trial focused on whether it was obvious to use pure EPA at the same dose, for the same period of time, to treat the same condition as Lovaza.

The district court found that it was. In its detailed 70-page opinion, which cited both sides' experts, the court concluded that a skilled artisan would have been

motivated to substitute pure EPA for Lovaza's EPA-DHA mixture to avoid Lovaza's known side effect of raising LDL-C ("bad" cholesterol). The court found this motivation because the prior art "taught that DHA increased LDL-C, whereas 4 g/day of 96% purified EPA reduced triglycerides without increasing LDL-C." Appx34. "The result of this obvious substitution"—pure EPA instead of mixed EPA-DHA—"is the method recited in all Asserted Claims." Appx57.

Amarin offers no legitimate basis to disturb the district court's judgment. It leads with secondary considerations, arguing that the court erred by "first considering a 'prima facie' case of obviousness," and then "consider[ing] the objective indicia, requiring them to 'overcome' the prima facie case." Br. 28. But this was not error. In a precedential decision directly on point, this Court held "it [i]s entirely appropriate" to first find "a prima facie case of obviousness" and "next consider whether [the] countervailing secondary consideration evidence … was sufficient to 'overcome' [the] prima facie case." *Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 719 F.3d 1346, 1353-54 (Fed. Cir. 2013). Yet Amarin does not even cite *Novo*, much less distinguish it.

Nor does Amarin ever acknowledge the district court's ultimate conclusion: "For the reasons discussed above, *in view of all four Graham factors (including alleged secondary considerations)*, Defendants have proven by clear and convincing evidence that all Asserted Claims are invalid as obvious under 35

U.S.C. § 103." Appx69 (emphasis added). Instead, Amarin mischaracterizes the court's opinion by arguing that it failed to evaluate secondary considerations before concluding the claims were obvious. In so arguing, Amarin ignores the court's explicit statement that it considered all four *Graham* factors before reaching its obviousness holding. Thus, Amarin's lead argument not only fails to cite contrary precedent—it fails to cite the district court's relevant conclusion.

Amarin is also incorrect to argue that the court "legally erred by pitting the categories of objective indicia against each other." Br. 45. The court simply found that certain alleged secondary considerations did "not weigh in favor of finding the Asserted Claims nonobvious." Appx66, Appx68-69. It did not find that the absence of these considerations favored obviousness.

Regardless, a "strong showing of obviousness may stand even in the face of considerable evidence of secondary considerations." *ZUP, LLC v. Nash Mfg., Inc.*, 896 F.3d 1365, 1374 (Fed. Cir. 2018) (quotation omitted). Here, the court found that Amarin's secondary-considerations evidence was far from "considerable." The court concluded that, "at best," Amarin's evidence was "weak." Appx69. Amarin thus fails to show any legal error, much less harmful error.

The rest of Amarin's brief merely rehashes factual arguments it made and lost below, which comes nowhere close to showing clear error. This Court gives "factual findings considerable deference on appeal," *Spectrum Pharm., Inc. v.*

Sandoz Inc., 802 F.3d 1326, 1336 (Fed. Cir. 2015), and "uphold[s] the trial court's determination if it is plausible in light of the entire record or where it chooses one of two permissible views of the evidence." *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 967 (Fed. Cir. 2006) (quotation omitted). "[T]he burden of overcoming the district court's factual findings is, as it should be, a heavy one." *Merck Sharp & Dohme Corp. v. Hospira, Inc.*, 874 F.3d 724, 728 (Fed. Cir. 2017).

Amarin cannot satisfy this heavy burden. The district court found that EPA's known ability to reduce triglycerides without raising LDL-C in patients with triglycerides below 500mg/dL was also reasonably expected in patients with triglycerides of at least 500mg/dL. Appx60-61. The district court credited Defendants' expert on this issue, a decision that "falls well within the wide discretion the court has to weigh expert credibility," which this Court upholds "absent compelling reason otherwise." *Senju Pharm. Co. v. Lupin Ltd.*, 780 F.3d 1337, 1351 (Fed. Cir. 2015). In finding that Amarin's expert's contrary position "lacks evidentiary support" (Appx60), the district court did not improperly "shift the burden." Br. ix. "[E]xplaining why a party's arguments are not persuasive does not constitute improper burden shifting." *Ignite USA, LLC v. CamelBak Prods., LLC*, 709 F. App'x 1010, 1016 (Fed. Cir. 2017).

Amarin's arguments to this Court contradict what Amarin previously told its regulator and investors. Before obtaining its own clinical data on EPA's effects on

severe hypertriglyceridemia, Amarin argued to FDA and investors that the prior art on EPA shows "no evidence of a significant rise in LDL-cholesterol," and "Multiple Studies Demonstrate that EPA is LDL Neutral." Appx90381, Appx90257. Amarin's witnesses agreed these statements were "truthful" and did not "mischaracterize" the prior art. Appx721(222:7-9), Appx712(213:19-25), Appx2629-2630(1835:4-1836:17). Amarin relied on this same prior-art evidence that EPA does not increase LDL-C when it applied for its patents, which contain no data, let alone clinical data on severe hypertriglyceridemia.

Amarin also concedes that a "rise in LDL-C generally was not observed in patients with" triglycerides as high as "499 mg/dL," even when such patients received fibrates, niacin, and EPA-DHA mixtures, which were known to raise LDL-C in some patients with severe hypertriglyceridemia. Br. 8. Amarin's expert admitted that 499mg/dL is "within error of the measurement" from 500mg/dL. Appx2614(1820:15-17). The district court recognized (Appx58-59) that this reasonable expectation of success at *exactly* 500mg/dL was enough to prove Amarin's claims obvious under the "long-established rule that claims which are broad enough to read on obvious subject matter are unpatentable even though they also read on nonobvious subject matter." *In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1281 (Fed. Cir. 2015) (quotation omitted).

Finally, even if Amarin could show harmful error (it cannot), the judgment below is supported by multiple alternative grounds for affirmance—the claims are not infringed, and are invalid for additional reasons. *Infra* 53-65. For any and all of these reasons, this Court should affirm.

COUNTER-STATEMENT OF ISSUES

I. Whether Amarin has shown reversible error in the district court's analysis of secondary considerations, where the court did not reach its obviousness conclusion until after it evaluated "all four *Graham* factors (including alleged secondary considerations)," and found as a factual matter that Amarin's secondary-considerations evidence was "weak." Appx69.

II. Whether Amarin has shown clear and reversible error in the district court's factual findings that the prior art would have motivated a skilled artisan to practice the claims with a reasonable expectation of success.

III. Whether the judgment is independently supported by alternative grounds of noninfringement and/or invalidity.

COUNTER-STATEMENT OF THE CASE

A. Lovaza, an EPA-DHA mixture, was approved to treat severe hypertriglyceridemia, but had a side effect of increasing LDL-C.

This case is about fish oil. In the 1970s, researchers discovered that fish-based diets were "linked to low incidence of coronary heart disease." Appx88501, Appx88505 nn.1-8; Appx90355. Through the 1980s, studies on "fish oils rich in

N-3 fatty acids were conducted and a reduction of plasma triglyceride levels was demonstrated." Appx88365, Appx88371 n.6. Scientists found that EPA and DHA—the "n-3" or omega-3 fatty acids in fish oil—"consistently reduce serum triglyceride levels." Appx88504. Based on these observations, fish oil has long been used to treat patients with hypertriglyceridemia.

Prior-art guidelines "define 'normal triglycerides' as less than 150 mg/dL, with levels above that considered elevated to various degrees." Appx3-4. "Severe hypertriglyceridemia" refers to patients having "levels above 500[mg/dL], regardless of why." Appx4. Doctors use triglyceride-lowering agents in patients with severe hypertriglyceridemia because it carries "an elevated risk of acute pancreatitis"—"an excruciatingly painful and potentially life-threatening condition." *Id*. At trial, "all experts agreed that the [500mg/dL] threshold simply represents a marker for the risk of pancreatitis, which has nothing to do with LDL-C levels." Appx60-61 (citing Appx2653(1859:3-13) (Toth)).

In 1997, a pharmaceutical-grade fish-oil product was developed in the United States. This product was initially called "Omacor," but was later renamed "Lovaza." Appx88356; Appx1344-1345(745:18-746:1) (Heinecke). By March 2008 (the alleged priority date), "Lovaza was 'widely used' and 'a very successful drug.'" Appx23 (quoting Appx2685(1891:7-12) (Toth)). The FDA-approved label for Lovaza was published in the "Physicians' Desk Reference," a well-known

compilation of drug labels, in 2007. Appx88408-88411 ("Lovaza PDR"). Lovaza PDR disclosed that Lovaza contained EPA and DHA. Appx23; Appx88409. Lovaza PDR further taught that Lovaza was clinically administered for 16 weeks, that its FDA-approved dose was 4g/day, and that it was "indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with very high (≥500 mg/dL) triglyceride levels." Appx88409-88410; Appx23-24.

Lovaza PDR warned that Lovaza "may result in elevations in LDL-C … in some individuals." Appx88410; Appx24. The district court found, and Amarin admits, that "doctors frequently prescribed LDL-C lowering statins to their patients with severe hypertriglyceridemia to address the LDL-C increases" associated with Lovaza. Br. 6; Appx24; Appx91708. However, "since 'those patients would have to take two pills, the Lovaza and a statin,' 'a skilled artisan would have been motivated to develop a single pill that treats severe hypertriglyceridemia without LDL-C increases.'" Appx57 (quoting Appx2616(1822:12-21) (Toth)) (citing Appx1412-1413(813:8-814:2) (Heinecke)).

B. The prior art taught that EPA, unlike DHA, reduces triglycerides without increasing LDL-C, and also reduces Apo B.

A "single pill" consisting of pure EPA was first sold in Japan in the 1990s by Mochida Pharmaceuticals as "Epadel." Appx88326. By 2000, "EPADEL capsules contain[ed] over 96.5%" pure EPA. Appx88401 (Kurabayashi). By January 2008, "99.9% [pure] EPA" was available. Appx58 (citing Appx88255). Epadel was

approved in Japan to treat "an excess of triglycerides," which includes severe hypertriglyceridemia. Appx88327; Appx1346-1347(747:17-748:8) (Heinecke).

Clinical studies in the prior art consistently found that EPA reduced triglycerides *without* increasing LDL-C. *E.g.*, Appx88589-88598 (Takaku); Appx88501-88504 (Nozaki); Appx88367, Appx88369 (Hayashi); Appx88349 (Grimsgaard); Appx88480-88485 (Mori); Appx88402-88403 (Kurabayashi); Appx1319-1321(720:14-722:1-4), Appx1323-1329(724:19-730:1), Appx1333-1334(734:4-735:20) (Heinecke). In contrast, "[m]ost previous studies of DHA supplementation have shown increases in LDL cholesterol." Appx88420 (Maki); Appx1343-1344(744:4-745:4) (Heinecke). The prior art thus "suggested that EPA and DHA have different properties against lipoprotein metabolism," including on LDL-C. Appx88501 (Nozaki); Appx1323(724:4-18) (Heinecke).

The differences between EPA and DHA were explored by Mori, who compared 4g/day EPA and 4g/day DHA. Appx88480-88483. As the district court found, "Mori taught that DHA increased LDL-C, whereas 4 g/day of 96% purified EPA reduced triglycerides without increasing LDL-C." Appx34. "Other prior art … similarly taught that EPA did not increase LDL-C in patients with triglyceride levels up to 400 mg/dL." *Id*. The prior art thus provided "very strong evidence that DHA, one of the two components of Lovaza …, is very likely responsible for

the increase in LDL," while "strongly suggest[ing] that EPA is [LDL-]neutral." Appx1344(745:1-9) (Heinecke).

Contrary to Amarin's arguments (Br. 8-13), EPA was not unique in reducing triglycerides in severely hypertriglyceridemic patients without raising LDL-C. Statins were known to have the same effect. Appx102640-102641; Appx2609-2611(1815:6-1817:8) (Toth); Appx1452(853:4-10), Appx1471-1472(872:17-873:18), Appx1509(910:8-17) (Heinecke). While Amarin cites examples of LDL-C increases from fibrates and Lovaza, this data involved patients with triglycerides above 700-800mg/dL, which is higher than the claimed 500mg/dL threshold. Appx108954-108955; Appx43940; Appx48910; Appx2611(1817:16-21), Appx2613-2615(1819:22-1821:2) (Toth). Regardless, data on fibrates, niacin, and Lovaza cannot be extrapolated to pure EPA, which is chemically unrelated to fibrates or niacin, and does not contain DHA. Appx2598(1804:2-20), Appx2595(1801:21-25) (Toth); Appx1400-1401(801:12-802:7), Appx1509-1511(910:21-912:4) (Heinecke); Appx88670.

The prior art also taught that EPA had other benefits apart from not raising LDL-C. In a 48-week controlled study by Kurabayashi, EPA significantly reduced Apo B, a marker for heart disease. Appx28-30; Appx88402, Appx88404. Two other prior-art studies likewise reported that EPA significantly reduced Apo B. Appx88349 (Grimsgaard); Appx88502 (Nozaki); Appx1323-1324(724:19-725:9),

Appx1327-1329(728:15-730:12), Appx1336-1337(737:1-738:25) (Heinecke). "Taken together, … these three studies provide very strong evidence that apo B levels can in fact be lowered by EPA." Appx1337(738:20-25) (Heinecke).

Additionally, a five-year clinical trial called "JELIS," which involved more than 19,000 patients and was published in *The Lancet*, found that EPA taken with statins reduced cardiovascular risk by 19% compared to statins alone, making EPA "a promising treatment for prevention of major coronary events." Appx88633; Appx1347-1349(748:9-750:5) (Heinecke); Appx90502.

Given the many studies on EPA and Epadel's commercial availability, dosing for EPA was well established by March 2008. A 2007 patent application by Mochida taught that EPA doses were "typically 0.3 to 6 g/day," with one "preferabl[e]" dose being "3.6 g/day"—i.e., about 4g/day. Appx88213; Appx1349-1350(750:6-751:4) (Heinecke). "[A]t least six prior art references … disclosed the use of 4 grams per day of purified EPA." Appx2649(1855:20-25) (Toth).

Although Amarin repeatedly argues "no one had even thought" to use EPA in severe-hypertriglyceridemia patients (Br. 17, 19, 36), at least five prior-art studies on pure EPA included patients with triglycerides ≥500mg/dL. Appx88367 (Hayashi: 300±233mg/dL); Appx88609 (Takaku: 650, 700, 1225mg/dL); Appx88445 (Matsuzawa: 1510mg/dL); Appx88543-88544 (Saito: 513mg/dL);

Appx88491 (Nakamura: 6.31mmol/L (≈560mg/dL)); Appx2656-2657(1862:23-1863:1) (Toth); Appx1351-1352(752:25-753:15) (Heinecke).

C. Amarin relied exclusively on prior-art studies to develop Vascepa.

Beginning in 2007, an Amarin employee named Mehar Manku made "contact with a scientist [at] Mochida [the maker of Epadel] to ask for their view of differences between pure EPA and EPA/DHA." Appx91241. Dr. Manku received "detailed information from Mochida on EPA's effects on LDL[-C]," and was told "Mochida haven't seen any increase in LDL[-C]." Appx90228, Appx90231.

In emails dated March 2008, Dr. Manku summarized what Mochida told him. As he explained, "we know from Japanese preclinical and clinical studies EPA does not increase LDL as [does] Omacor [i.e., Lovaza]." Appx90691. Citing prior-art studies, he observed that "LDL cholesterol has not been reported to rise after pure EPA," and "publications from M[o]chida on EPADEL" showed "LDL-[C] is reduced." Appx90238, Appx90566. These emails summarizing the prior art are the only evidence Amarin cited during discovery to support its alleged conception date of March 25, 2008. Appx109201; Appx91491 n.13.[1]

[1] Amarin now tells a different story—that Dr. Manku "conceived" that EPA would not raise LDL-C based on Amarin's failed, unpublished studies on central-nervous-system disorders. Br. 18-20. This conception story was not disclosed in discovery and is waived. Regardless, it is meritless. Amarin told FDA its CNS studies found "[n]o consistent changes in triglyceride and cholesterol levels," "were not designed to recruit and evaluate patients with high triglyceride levels," and did not measure

Even before this alleged conception date, an Amarin memo dated March 10, 2008, recognized that "[i]n view of the extensive clinical experience with ultra pure EPA … only further limited clinical data are required to confirm the efficacy and safety of ethyl-EPA as a treatment of severe hypertriglyceridemia." Appx90295. Another memo dated March 20, 2008, acknowledged Epadel was "identical" to Vascepa (then called "AMR101"), and that the "one differentiating feature" between Epadel and Lovaza "is their respective effect on LDL." Appx90421, Appx95532. While "Lovaza treatment may result in elevations in LDL in some individuals," "Epadel treatment does not appear to have the same [e]ffect on LDL levels…. Hence there is no reference to Epadel treatment causing LDL elevation in Epadel's packaging insert." Appx90421-90422. This was confirmed by "Mochida's studies on Epadel, as well as independent studies." Appx90422. As Amarin recognized, Mori taught that while "both EPA and DHA reduced triglycerides," only "DHA was also associated with an increase in LDL cholesterol." Appx90428.

In June 2008, less than three months after Amarin's alleged conception date and more than two years before it had any clinical data of its own on

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blood levels "in a fasting state," among other "major limitations." Appx90362. There is "no connection whatsoever" between "the CNS effects of EPA" and severe hypertriglyceridemia. Appx1512(913:12-23) (Heinecke).

hypertriglyceridemia, Amarin told FDA that a "large body of evidence supports the efficacy of Ethyl-EPA, administered either as monotherapy or add-on to statin therapy, in reducing triglyceride levels in patients with dyslipidemia of varying severity." Appx90362. Amarin represented that "[i]n clinical studies performed with Ethyl-EPA to date … there is no evidence of a significant rise in LDL-cholesterol." Appx90381. Amarin's corporate representative, Dr. Ketchum, confirmed "Amarin had not yet conducted any clinical studies" on hypertriglyceridemia when it made these statements to FDA, which were "candid and truthful." Appx725(226:7-13), Appx721(222:7-9).

In 2009, Amarin continued relying on Mori to promote Vascepa. Appx90860. In a partnering presentation, Amarin described Mori in a slide titled "EPA—No LDL Effect." Appx90904. Dr. Toth admitted this presentation "told [Amarin's] potential partner that Mori teaches that 96 percent EPA, 4 grams per day, has zero percent change in LDL." Appx2626-2627(1832:8-1833:1). He further admitted this presentation "did not misrepresent Mori." *Id*.

In March 2010, still months before Amarin had its own data on hypertriglyceridemia, Amarin cited prior art to convince investors of a "Clear Differentiation between [Vascepa] and Lovaza." Appx90254; Appx2627(1833:4-19) (Toth). Amarin assured investors that Vascepa causes "[n]o DHA induced elevation" of LDL-C. Appx90254. As proof, Amarin cited prior art—including

Mori and Kurabayashi—in slides titled "Multiple Studies Demonstrate that DHA Raises LDL-C" and "Multiple Studies Demonstrate that EPA is LDL Neutral":

Multiple Studies Demonstrate that DHA Raises LDL-C

Study author and year	DHA treatment	Treatment duration	Baseline TG	Change in TG	Baseline LDL mg/dl	Change in LDL
Kelley 2007	3g	90 days	248	-24.4%	120	+13.5%
Maki 2005	1.5g	6 weeks	179	-21.4%	142	+12.0%
Theobald 2004	1.5g	3 months	92	-2%	122	+10.1%
Geppert 2006	2.28g	8 weeks	96	-23.2%	95	+10.6%
Sanders 2006	1.5g	4 weeks	96	-13.9%	97	+6.7%
Engler 2004	1.2g	6 months	139	-9.9%	201	+14%
Nestel 2002	2.8g	7 weeks	176	-32%	176	+3.8%

Multiple Studies Demonstrate that EPA is LDL Neutral

Study author and year	EPA treatment	Treatment duration	Baseline TG	Change in TG	Baseline LDL mg/dl	Change in LDL
Kurabayashi 2000	1800	48 weeks	136	-13.8%	165	-5.88%
Yamashita 1995	1800	8 weeks	161	-24.8%	139.5	-4.66%
Ando 1999	1800	3 months	260	-42.1%	144	-15.72%
Mori 2000	4000	6 weeks	179	-18.4%	172	0.00%
Grimsgaard 1997	4000	7 weeks	109	-12.2%	158	-1.97%
Woodman 2002	4000	6 weeks	119	-17.1%	104	0.75%

Appx90256-90257. Amarin's fact and expert witnesses confirmed these representations were "accurate," "truthful," and did not "mischaracterize[]" the prior art. Appx709-710(210:20-211:10), Appx714-715(215:25-216:12) (Ketchum); Appx2630(1836:2-17) (Toth).

Amarin did not obtain its own data on EPA's effects in severely hypertriglyceridemic patients until it completed its "MARINE" study in late 2010, more than a year after filing its patent application. Appx2587(1793:2-4) (Toth). Amarin published these results in the Bays article, which recognized that prior-art studies "suggested that purified EPA might reduce TG levels without increasing the LDL cholesterol levels," because "although DHA treatment generally increased LDL cholesterol levels, EPA therapy did not." Appx90090, Appx90096. Among other prior art, Bays cited Mori and Kurabayashi. Appx90098 nn.7, 15; Appx2632-2634(1838:5-1840:18) (Toth).

Although Bays states the lack of LDL-C increases in MARINE was "unexpected" (Appx90096), its lead author, Dr. Bays, disagreed. Before the article was published, Amarin emailed him about adding the "unexpected" language, which was "very important for Amarin." Appx90055; Appx90070. Dr. Bays objected to this addition because "the statement … that this finding was 'unexpected' is in contradiction to the rest of the manuscript"—and "largely guts … the reality of this drug development program." Appx90088.

Amarin continued relying on Mori even after FDA approved Vascepa. In 2014, Amarin told FDA that "[t]he data from [Mori] support … that EPA and DHA have differential effects on other well-studied lipid parameters such as LDL-C." Appx94505-94506 & n.59; Appx716-719(217:13-220:9) (Ketchum).

D. Amarin mischaracterized prior art during prosecution, but the examiner still found the claims prima-facie obvious.

In February 2009, more than a year before Amarin had any data on EPA's effects in severely hypertriglyceridemic patients, Amarin filed a provisional application that eventually issued as the six patents-in-suit. The patents' common specification contains no data. Appx73-207; Appx2593-2595(1799:11-1801:11) (Toth). Instead, it recites laundry lists of possible clinical effects in addition to triglyceride reduction, including no impact on, or a reduction in, LDL-C and Apo B. Appx87-88(5:15-7:44). The 10 asserted claims, which recite some of these possible clinical effects, all require the same method of treatment—administering 4g/day of pure EPA for at least 12 weeks to a patient with triglycerides ≥500mg/dL. Appx10-13.

The examiner repeatedly found these claims obvious. Among other references, the examiner cited Hayashi, which he found taught the administration of EPA "to individuals with serum TG levels of 300 ± 233 mg/dl (i.e. between 67 mg/dl and 533 mg/dl)." Appx88683. Partly because these levels "overlap with the claimed ranges of serum TG," the examiner found "a *prima facie* case of obviousness." Appx88684. "Further, all the other variables claimed, like amount administered (4 g), period of treatment (12 weeks), purity of EPA-E (at least about 96%) are either similar or overlap with the data disclosed by the prior art," which Amarin did not dispute. Appx88685.

Amarin tried "to overcome the obviousness rejection" with secondary considerations, but they were "not sufficient." Appx88699. Given Hayashi, the examiner found that "[t]he prior art clearly teaches" the administration of pure EPA to "patients with TG levels … up to 530 mg/dl." *Id*. Amarin's secondary considerations were "not enough to overcome such a strong case of obviousness." Appx88700.

To overcome Hayashi, Amarin submitted a declaration from Phillip Lavin, a statistician. Appx88703-88706. Dr. Lavin opined that "not even one patient in [Hayashi] would be expected to have a TG level of 450 mg/dl or higher." Appx88704. Citing Dr. Lavin, Amarin argued that "it is not reasonable for the Office to allege that any of the subjects in Hayashi have baseline TG levels that overlap with the presently claimed range." Appx87913. Amarin reasserted that "[e]ven if a *prima facie* case has been established," secondary considerations would rebut it. Appx87922.

In his notice of allowance, the examiner accepted Dr. Lavin's opinion that "[t]he prior art does not teach the administration of ethyl-EPA to patients having TG levels between 500 and 1500 mg/dl (very high)." Appx88716. The examiner still found it "obvious to treat patients having TG above 500 mg/dl with 96% pure ethyl-EPA." *Id*. But now, without a finding that EPA was given to patients with severe hypertriglyceridemia, the examiner did not characterize his prima-facie

finding as "strong." Thus, Amarin "was able to overcome the … obviousness rejection" with alleged secondary considerations. Appx88717.

It is now beyond dispute that Dr. Lavin's opinions about Hayashi were mistaken. Dr. Lavin admitted he would "rewrite" his declaration, because "there must be at least one subject" with triglycerides above 500mg/dL in Hayashi, and it is "likely that you have one or two observations above 533[mg/dL]." Appx4095-4096(102:24-103:21); Appx26-27. Dr. Toth did not "offer any type of statistical opinion to corroborate what Dr. Lavin told the patent office." Appx2662(1868:13-16). And Dr. Toth admitted that four other prior-art references, which the examiner overlooked, each had "at least one patient … with triglycerides over 500." Appx2656-2657(1862:23-1863:1); *supra* 11-12; Appx1351-1355(752:10-756:14) (Heinecke).

E. Based on a battle of experts at trial, the district court found clear and convincing evidence that all asserted claims are invalid.

By characterizing pure EPA as a "new chemical entity" and then suing Defendants under the Hatch-Waxman Act, Amarin obtained seven-and-a-half years of regulatory exclusivity for Vascepa. 21 U.S.C. §355(j)(5)(F)(ii).

After four years of litigation and a seven-day trial, the district court issued a 70-page opinion holding all asserted claims obvious. Before reaching any conclusions regarding obviousness, the court recognized it "must also consider whether objective indicia of non-obviousness support the Asserted Claims," and

analyzed Amarin's evidence on that issue. Appx35-44. After reciting the four-factor test under *Graham*, the court acknowledged that Defendants "bear the ultimate burden of proving, by clear and convincing evidence, that the Asserted Claims are invalid." Appx54-55. The court also recognized "it is not permissible to use hindsight … or to rely at all on the teachings of the claimed invention" in evaluating obviousness. Appx33.

Under a heading titled "Prima Facie Obviousness," the court found that Amarin "concede[d] a number of Defendants' key premises." Appx57. "[T]here [wa]s no dispute that the only difference between the method in the Lovaza PDR and the method in the asserted claims is that Lovaza contained a mixture of EPA and DHA, instead of purified EPA." *Id*. "Nor [wa]s there any dispute that the increases in LDL-C caused by Lovaza were known, and that 'a skilled artisan would have been motivated to avoid LDL-C increases when treating patients with severe hypertriglyceridemia.'" *Id*.

Citing Dr. Toth's admissions, the court found 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." *Id*. "Dr. Toth did not dispute 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.'" *Id*. (quoting

Appx2581(1787:6-10)). "Nor did he dispute that 'Mori found that the increase of LDL-C with DHA was statistically significant and the increase with EPA was not.'" Appx57-58 (quoting Appx2582(1788:18-25)). Thus, "the key premises that he conceded lead directly to the motivation to combine and reasonable expectation of success." Appx58.

The court considered Amarin's factual counterarguments but found them "unavailing." Appx59. It rejected Amarin's "factual premise that lacks evidentiary support—that patients with TG levels above 500 mg/dL respond differently to TG-lowering therapy than patients with TG levels below 500 mg/dL." Appx60. The court found that "even if Mori and other studies on patients with lower TGs did not provide 'conclusive proof' of EPA's effects, they were enough to form 'a reasonable expectation of success.'" *Id*. (quoting *Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014)). The court credited Dr. Heinecke's testimony that "there is no 'magical mechanistic difference' between having triglycerides of 400, 500, or 600 mg/dL," especially since "[a] skilled artisan would understand that, regardless of a patient's baseline triglycerides, 'the qualitative effects of medications … tend to be the same.'" Appx60-61 (quoting Appx1395(796:5-20), Appx1396(797:16-18)).

The court thus found that "Defendants established by clear and convincing evidence at Trial that all Asserted Claims are *prima facie* obvious." Appx59;

Appx61. Emphasizing it had not yet reached its obviousness conclusion, the court reiterated that "evidence rising out of the so-called 'secondary considerations' must always when present be considered en route to a determination of obviousness." Appx61 (quotation omitted). In total, the court devoted 18 pages to analyzing alleged secondary considerations before reaching its ultimate conclusion of obviousness. Appx35-44, Appx61-69.

Most of Amarin's secondary-considerations evidence focused on its "REDUCE-IT" study, which confirmed EPA's ability to reduce cardiovascular risk. The court, however, found that REDUCE-IT lacks a nexus to the asserted claims—a finding that Amarin and its amici do not dispute. Appx61-66. The court also found the claims were not supported by unexpected results, skepticism, or praise. Appx66-69, Appx42-44. The only secondary considerations the court found were long-felt need, "weigh[ing] slightly in favor of" nonobviousness, and commercial success. Appx67, Appx69. But the court did not consider whether Vascepa's commercial success has a nexus to the claims. Overall, the court found that Amarin's secondary-considerations evidence was "weak." Appx69.

At the end of its opinion, for the first time, the court reached its obviousness conclusion: "in view of all four *Graham* factors (including alleged secondary considerations), Defendants have proven by clear and convincing evidence that all

Asserted Claims are invalid as obvious under 35 U.S.C. § 103." *Id.* Amarin never quotes this conclusion in its brief.

SUMMARY OF ARGUMENT

I.A. Amarin's lead argument—that the district court "erroneously bifurcated a 'prima facie' case of obviousness and the objective indicia of non-obviousness" (Br. 31)—is legally and factually flawed. Legally, a finding that "prima facie evidence, if unrebutted, would be sufficient to establish" obviousness is "entirely appropriate." *Novo*, 719 F.3d at 1354. Factually, Amarin ignores the district court's holding, which considered "all four *Graham* factors (including alleged secondary considerations)." Appx69. Nor did the court hold that any secondary consideration was "'outweighed' by the purported failure to prove another." Br. 45. The court simply found—correctly—that Amarin's evidence "does not weigh in favor of … nonobvious[ness]." Appx66, Appx68-69.

I.B-C. Regardless, any alleged legal error in the court's secondary-considerations analysis would be harmless. Given Amarin's "weak evidence of … secondary considerations" (Appx69), the claims are invalid no matter how that evidence is weighed. While Amarin relies heavily on Vascepa's commercial success, it never articulates a nexus to the claims. Nor could it—Amarin's expert admitted that the claimed treatment of severe hypertriglyceridemia accounts for only "25 percent of the sales of Vascepa." Appx2195(1497:4-23). The remaining

75% are for cardiac benefits in patients with lower triglycerides, which are not covered by the claims. Nor does Amarin show any clear error in the court's factual findings on other secondary considerations. The record amply supports the conclusion that Amarin's evidence was "weak." Appx69.

II.A. Amarin's challenges to the district court's findings on motivation and reasonable expectation of success—pure questions of fact—are equally flawed. Amarin challenges the finding that EPA was reasonably expected to lower triglycerides without raising LDL-C in severely hypertriglyceridemic patients. But the court's findings are supported by the record, including expert testimony. In arguing otherwise, Amarin ignores that "conclusive proof" of EPA's effects was not required to find obviousness—especially since Amarin's "patents do not themselves present [any] data." *Hoffmann*, 748 F.3d at 1331.

II.B-C. Amarin's arguments that the court "ignored" its evidence and "shifted the burden" also lack merit. The court considered Amarin's positions but correctly found they "lack[] evidentiary support." Appx60. Indeed, unable to cite evidence that *EPA* raises LDL-C, Amarin cited irrelevant data on *different* products—with no evidence that those results could be extrapolated to EPA, much less in patients with triglycerides of exactly 500mg/dL. The district court did not err in rejecting Amarin's contrived argument.

III. Even if Amarin could show harmful error, multiple alternative grounds warrant affirmance. First, seven of the 10 asserted claims cover the combined use of EPA with a statin. Statins were admittedly expected to reduce triglycerides without raising LDL-C. Thus, these claims would be obvious even accepting Amarin's arguments about EPA alone. The remaining three claims, which exclude concurrent lipid-altering therapies like statins, are not infringed. Amarin's sole infringement theory at trial was that the labels for Defendants' accused products induce infringement. But nothing in the labels even mentions, let alone requires, excluding concurrent-lipid altering therapy. Thus, there is no inducement.

Second, Defendants do not induce infringement of *any* claim, all of which require administering EPA for at least 12 weeks. There is no instruction for 12-week use in Defendants' labels, which Amarin's experts admitted "leave it entirely up to the physician's discretion to determine the duration of treatment." Appx991(444:8-11).

Third, even if Amarin were right that skilled artisans lacked a reasonable expectation of success in patients with severe hypertriglyceridemia, the claims would be invalid for lacking written description. Amarin's patents contain no data or other evidence suggesting that EPA reduces triglycerides without raising LDL-C or reduces Apo B in patients with triglycerides ≥500mg/dL. Thus, if Amarin were correct that the prior art provided no basis to believe that EPA would produce these

effects, Amarin likewise possessed no "invention" when it filed for its patents, which are based entirely on the prior art.

STANDARD OF REVIEW

"Obviousness is a question of law, reviewed *de novo*, based upon underlying factual questions which are reviewed for clear error." *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1289 (Fed. Cir. 2006). "The presence or absence of a motivation to combine references in an obviousness determination is a pure question of fact, as is the presence or absence of a reasonable expectation of success." *Id*. (citations omitted). "Under the clear error standard, a reversal is permitted only when this court is left with a definite and firm conviction that the district court was in error." *Id*.

Even the presence of "legal and factual errors in the district court's opinion," however, "does not, in itself, compel reversal." *Wavetronix LLC v. EIS Elec. Integrated Sys.*, 573 F.3d 1343, 1345 n.1 (Fed. Cir. 2009). "This court sits to review judgments, not opinions." *Id*. "[C]orrection of an error must yield a different result in order for that error to have been harmful." *Munoz v. Strahm Farms, Inc.*, 69 F.3d 501, 504 (Fed. Cir. 1995).

"Appellees always have the right to assert alternative grounds for affirming the judgment that are supported by the record." *MEHL/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1366 (Fed. Cir. 1999). "Where, as here, the district

court has entered a judgment of invalidity as to all of the asserted claims, … (1) additional claims for invalidity or (2) claims of non-infringement" are "alternate ground[s] for affirming the district court's judgment." *TypeRight Keyboard Corp. v. Microsoft Corp.*, 374 F.3d 1151, 1157 (Fed. Cir. 2004).

ARGUMENT

I. Amarin fails to show harmful error in the district court's secondary-considerations analysis.

As shown below, Amarin fails to prove any legal error in the district court's secondary-considerations analysis. Even if such legal errors existed, they would be harmless given the district court's factual findings that, "at best," Amarin's secondary-considerations evidence was "weak." Appx69. In challenging those findings, Amarin fails to satisfy the clear-error standard. Accordingly, the judgment should be affirmed.

A. Amarin's attempts to manufacture legal error lack merit.

1. The district court did not "shift the burden"—it followed on-point precedent that Amarin fails to cite.

Amarin admits that the district court's use of "the words 'prima facie case' in conducting an obviousness analysis" was not "error." Br. 44. Amarin also admits that the district court cited "this Court's precedents regarding secondary considerations—stating that they must be considered." Br. 43. Amarin nonetheless argues that the court "improperly shift[ed] the burden of persuasion to Amarin" by "first consider[ing] only an erroneous 'prima facie' case of

obviousness," and then "asking whether the objective indicia evidence 'overc[a]me the Court's finding that all Asserted claims are prima facie obvious.'" Br. 42-43 (quoting Appx69). But Amarin is wrong.

In *Novo*—a case that Amarin ignores completely—this Court rejected the identical argument that Amarin makes here and concluded that the district court did not reach a premature conclusion on obviousness before considering objective indicia. 719 F.3d at 1354. "The mere fact that the court conducted this analysis using terms such as 'overcome' and 'prima facie' does not necessarily imply that it shifted the burden of persuasion." *Id.* at 1353-54. "[T]his language simply reflects the court's shift of the burden of production once the court determined that the challenger has established a prima facie case of obviousness," which is "entirely appropriate." *Id.* at 1354.

This Court has repeatedly affirmed similar district-court decisions holding that "objective indicia do not overcome" a "strong prima facie showing." *Intercontinental Great Brands LLC v. Kellogg N. Am. Co.,* 869 F.3d 1336, 1345-46 (Fed. Cir. 2017); *Cubist Pharm., Inc. v. Hospira, Inc.*, 805 F.3d 1112, 1130 (Fed. Cir. 2015) ("We sustain the district court's determination that the secondary consideration evidence did not overcome the showing of obviousness based on the prior art."); *Tokai Corp. v. Easton Enters., Inc.*, 632 F.3d 1358, 1371 (Fed. Cir. 2011) ("A strong case of prima facie obviousness, such as that presented here,

cannot be overcome by a far weaker showing of objective indicia of nonobviousness."); *see also Valeant Pharm. Int'l, Inc. v. Mylan Pharm. Inc.*, 955 F.3d 25, 33 (Fed. Cir. 2020) ("Mylan has at least raised a prima facie case of obviousness"; "the factfinder should consider whether Valeant has rebutted Mylan's prima facie case."); *Persion Pharm. LLC v. Alvogen Malta Operations Ltd.*, 945 F.3d 1184, 1194 (Fed. Cir. 2019) ("While the district court's discussion of objective indicia follows its discussion of the asserted prior art, the substance of the court's analysis makes clear that it properly considered the totality of the obviousness evidence."). Again, Amarin cites none of these cases.[2]

Instead of addressing *Novo*, Amarin relies on *In re Cyclobenzaprine*, which preceded and was distinguished by *Novo*. 719 F.3d at 1352-54. *Cyclobenzaprine* is also distinguishable here. There, "[b]efore it reached the objective considerations, the district court stated that the claimed [invention] 'would have been obvious to one of skill in the art at the time of the invention.'" 676 F.3d 1063, 1075 (Fed. Cir. 2012). The court thus failed to "withhold judgment on an

[2] Unlike Amarin, its amicus BIO acknowledges that *Novo* and other precedential cases endorse this "prima facie framework." BIO Br. 6, 9. To the extent BIO asks the Court to overrule *Novo*, that is not a proper request for this panel. "This court respects the principle of stare decisis and follows its own precedential decisions unless the decisions are 'overruled by the court en banc, or by other controlling authority such as an intervening ... Supreme Court decision.'" *Teva Pharm. USA, Inc. v. Novartis Pharm. Corp.*, 482 F.3d 1330, 1338 (Fed. Cir. 2007).

obviousness challenge until it consider[ed] all relevant evidence, including that relating to the objective considerations." *Id.* at 1079.

By contrast, here, the district court merely found the claims "prima facie obvious," but did not pass judgment on the ultimate issue of obviousness until it analyzed "all four *Graham* factors (including alleged secondary considerations)." Appx59, Appx69. The court further recognized that proffered evidence of secondary considerations "must always when present be considered en route to a determination of obviousness." Appx61 (quotation omitted). The court devoted 18 pages of its 70-page opinion to analyzing Amarin's proffered secondary-considerations evidence. Appx35-44, Appx61-69. These pages included nine pages of factual findings concerning secondary considerations that *preceded* any mention of prima-facie obviousness. Appx35-44. Thus, the court did not improperly shift the burden of persuasion to Amarin.

2. The district court did not use Amarin's alleged secondary considerations as affirmative evidence of obviousness—it found them unpersuasive and "weak."

Amarin also argues that the district court "legally erred by pitting the categories of objective indicia against each other." Br. 45. This argument is based on a single sentence in the district court's opinion stating that evidence of long-felt need and commercial success were "outweighed by the fact that the Court found Plaintiffs' other proffered secondary considerations favor Defendants." Appx69.

But Amarin takes this statement out of context. The next sentence makes clear that the court's comment was simply a lead-in to its factual determination that Amarin "presented weak evidence of the existence of secondary considerations." *Id.* This finding is consistent with its earlier finding that long-felt need only "weighs slightly in favor of finding the Asserted Claims nonobvious." Appx67.

Amarin is also wrong to argue that the court relied on the absence of unexpected results, skepticism, and praise to find obviousness. Br. 45. Rather, the court expressly found that Amarin's alleged evidence of unexpected results, skepticism, and praise "does not weigh in favor of … nonobvious[ness]." Appx42, Appx66, Appx68-69. Amarin never cites these statements. The district court further found that Amarin's "weak evidence" of secondary considerations did not overcome Defendants' "'strong showing of obviousness'" based on the prior art, which is consistent with this Court's precedent. Appx69 (quoting *ZUP*, 896 F.3d at 1373). Amarin has shown no legal error in the district court's analysis.

B. Amarin's alleged legal errors would be harmless.

1. The claims would be obvious even if the district court had given commercial success and long-felt need greater weight.

Even if Amarin could show legal error, any error would be harmless. Amarin ignores that "mischaracterization of the burden of proof in an opinion, by itself, does not warrant reversal." *ISCO Int'l, Inc. v. Conductus, Inc.*, 123 F. App'x 974, 977 (Fed. Cir. 2005). Even "misstat[ing] the law at various points does not …

require reversal" so long as the record contains "sufficient evidence to support the judgment." *Pentec, Inc. v. Graphic Controls Corp.*, 776 F.2d 309, 317 (Fed. Cir. 1985); *see also Union Carbide Corp. v. Am. Can Co.*, 724 F.2d 1567, 1573-74 (Fed. Cir. 1984) ("[W]e cannot reverse unless, under the §103 standard, the result, as opposed to the reasoning, is erroneous.").

Amarin's cited cases are consistent with this principle. In *Stratoflex* (Br. 42), the district court outright "refus[ed] to include" secondary considerations in its analysis—a far cry from this case. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1540 (Fed. Cir. 1983). Even in the face of this refusal, this Court held that the court's error was "harmless" because "nonobviousness [wa]s not established by that evidence." *Id*.

In Amarin's other cited cases (Br. 46), the failure to credit secondary considerations also was not, by itself, reversible error. Rather, the outcome in all these cases turned on clear factual errors. *Cyclobenzaprine*, 676 F.3d at 1069 (finding "clear error in a number of the district court's factual findings"); *Millennium Pharm., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1364 (Fed. Cir. 2017) ("The district court clearly erred" because there was "no teaching or suggestion in the references to produce the claimed [invention]."); *Institut Pasteur v. Focarino*, 738 F.3d 1337, 1344 (Fed. Cir. 2013) (PTAB "made factual determinations that were not supported by substantial evidence"). Thus, these cases are

distinguishable. As explained below, Amarin fails to show any clear error in the district court's factual findings, which credited Dr. Heinecke's opinions as "persuasive," found that Dr. Toth conceded "key premises … that lead directly to the motivation to combine and reasonable expectation of success," and rejected Amarin's counterarguments as "unavailing." Appx57-59.

Given the court's factual finding that Defendants presented a strong prima-facie case, Amarin's alleged secondary considerations would not avoid obviousness here. *E.g.*, *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 35 (1966) ("[T]he long-felt need in the industry for [the invention] together with its wide commercial success supports its patentability.… However, these factors do not, in the circumstances of this case, tip the scales of patentability."); *Merck*, 874 F.3d at 731 (affirming obviousness despite error weighing secondary considerations—"even giving the evidence of commercial success its full and proper weight, the court did not err in concluding that the claims would have been obvious"); *Bayer Pharma AG v. Watson Labs., Inc.*, 874 F.3d 1316, 1329 (Fed. Cir. 2017) (claims were obvious despite "copying and unexpected results that weigh in favor of a conclusion of nonobviousness").

2. Vascepa's alleged commercial success cannot weigh in favor of nonobviousness because it lacks a nexus to the claims.

Any legal error in the court's weighing of secondary considerations is also harmless because there is no nexus between Vascepa's alleged commercial success

and the claims. Because the district court found strong evidence of obviousness, the issue of nexus was immaterial to the court's decision. Nevertheless, the lack of nexus is an independent basis to affirm.

"[F]or commercial success to be probative evidence of nonobviousness, a nexus must be shown between the claimed invention and the evidence of commercial success." *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1363 (Fed. Cir. 2012). Where "the evidence does not show that the success of [the] product was directly attributable to [the claimed invention]," commercial success should be "discounted." *Id.* at 1364.

Here, Amarin's commercial-success expert admitted that only "one-third of the sales of Vascepa, from 2013 to 2018, related to patients with severe hypertriglyceridemia." Appx2195(1497:4-7). By 2018, only "25 percent of the sales of Vascepa related to patients that have TG levels of 500 or more." Appx2195(1497:12-23); Appx108947. Likewise, both sides' clinical experts agreed that only a small minority of Vascepa prescriptions are written for severe hypertriglyceridemia. Most are written for reducing cardiovascular risk in patients with triglycerides as low as 150mg/dL, which has "an insufficient nexus" to the claims. Appx66; Appx1055-1056(508:12-509:9) ("85 percent of [Dr. Budoff's Vascepa] patients did not ever have triglycerides above 500"); Appx1137(590:7-9)

("70 some odd percent of [Dr. Sheinberg's Vascepa] patient population is characterized [by] the [cardiovascular-risk] indication for REDUCE-IT").

"As the patentee, it was [Amarin]'s burden of production to demonstrate a nexus between the claimed [invention] and the secondary considerations." *MRC Innovations, Inc. v. Hunter Mfg., LLP*, 747 F.3d 1326, 1336 (Fed. Cir. 2014). Yet Amarin's brief never addresses this issue. Because Vascepa's "success" is not "directly attributable" to the claimed treatment of severe hypertriglyceridemia, it must be "discounted … as a secondary consideration." *Wrigley*, 683 F.3d at 1364.

C. Amarin shows no clear error in the district court's rejection of alleged secondary considerations.

Unable to show any legal error in the district court's obviousness analysis, Amarin argues that the district court "clearly erred in finding a lack of skepticism and praise," and "failed to give proper weight" to long-felt need and the age of prior-art references. Br. 34, 37. But these arguments do not remotely pass muster under the clear-error standard, which demands "considerable deference on appeal" to the district court's factual findings. *Spectrum*, 802 F.3d at 1336.

Skepticism. Amarin "did not present any expert testimony at Trial regarding skepticism" as to EPA's effects on LDL-C (Appx68), and its post-trial brief never mentioned this issue. Amarin only asserted skepticism for Vascepa's cardiovascular effects. Appx103405. The court found that these effects lack a nexus to the claims (Appx61-66)—a finding Amarin does not appeal. The court

nevertheless considered whether there was LDL-C-related skepticism and correctly found none. Indeed, the only purported evidence of skepticism was one line in an inventor's unpublished notes referring to the LDL-C effects of "virtually all tg lowering therapies," which Amarin attributes to an unidentified speaker on "a panel of experts hired by Amarin." Appx68, Appx47720, Br. 38. For the first time on appeal, Amarin cites "additional … contemporaneous notes" to bolster its claim of skepticism. Br. 39-40. Putting aside waiver, this "evidence" at best suggests "lack of enthusiasm by a few[,] [which] is not equivalent to skepticism." *BTG Int'l Ltd. v. Amneal Pharm. LLC*, 923 F.3d 1063, 1076 (Fed. Cir. 2019).

Praise. Amarin's evidence of "praise" is equally weak, consisting of one doctor's statement in a single article. Br. 40 (citing Appx88650). The court correctly found that even this single doctor did not give "unmitigated praise," but "expressed caveats." Appx42. Nor does Amarin acknowledge that the article quoted another doctor who "did not praise Vascepa or MARINE, but instead dismissed MARINE's significance because typical increases in LDL-C with Lovaza were 'modest' and 'not that big an issue,' especially since Lovaza 'works well with statins.'" Appx42-43 (quoting Appx88650). Such "conflicting statements" do not establish "praise[] by the industry." Appx43.

Long-felt need. Amarin disputes the court's finding that long-felt need weighed only "slightly" toward nonobviousness. Appx67. But this finding too is

not clearly erroneous. Amarin alleges an "unmet need" to avoid raising LDL-C, yet admits there was a "previous answer to this problem—prescribing a statin." Br. 37; Appx91708. Amarin says this answer "was inadequate" because patients are "less likely to take two pills rather than just one." Br. 37. But the district court found this was simply a reason why skilled artisans "would be motivated to combine the Lovaza PDR with the finding from Mori that EPA did not raise LDL-C levels." Appx67. Without more, such motivation does not establish probative long-felt need. *Cf. Celgene Corp. v. Peter*, 931 F.3d 1342, 1353-54 (Fed. Cir. 2019) ("The fact that there is no long-felt, unmet need does not necessarily mean that there is no motivation.").

Amarin also faults the court for "dismiss[ing]" the fact that "the 'Asserted Claims represent an improvement.'" Br. 37 (quoting Appx67). But whether the invention "may be preferable to" the prior art is "insufficient … to establish a long-felt need." *Par Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1200 (Fed. Cir. 2014). Rather, evidence must "show that [the prior art's] drawbacks constituted a long-felt, unmet need," "'analyzed as of the date of an articulated identified problem.'" *Perfect Web Techs., Inc. v. InfoUSA, Inc.*, 587 F.3d 1324, 1332-33 (Fed. Cir. 2009). Here, no prior art "articulate[d]" or "identifie[d]" a need to avoid co-administering statins with EPA or DHA.

Passage of time. Amarin next argues that "pure EPA products had been on the market in Japan for over fifteen years," yet "no one before Dr. Manku thought to use this supposedly obvious way to treat severely hypertriglyceridemic patients." Br. 35-36. But this is a clear misrepresentation. As the court found, and Dr. Toth admitted, pure EPA *was* used to treat severely hypertriglyceridemic patients in the prior art. Appx26-27; Appx2656-2657(1862:23-1863:1). And there is no evidence of a single instance of LDL-C increases in such patients.

Regardless, "mere passage of time without the claimed invention is not evidence of nonobviousness." *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1325 (Fed. Cir. 2004). That is especially true here since severe hypertriglyceridemia is "rare," and statins were "extremely well tolerated." Appx88309, Appx1408-1409(809:21-810:14) (Heinecke). Indeed, Amarin admits that severe hypertriglyceridemia affects only "3.5 million Americans"—about 1% of the population. Br. 4. In such "a niche market, it is not surprising that it took a few years for a company to expand on the prior art." *Tokyo Keiso Co. v. SMC Corp.*, 307 F. App'x 446, 453 (Fed. Cir. 2009).

It was not until JELIS taught in 2007 (one year before the alleged invention) that EPA is "a promising treatment for prevention of major coronary events," that there was a major *commercial* incentive to pursue pure EPA in the United States. Appx88633; Appx2697(1903:5-17) (Toth). The market for cardiovascular-risk-

reduction is considerably larger than that for severe hypertriglyceridemia. As Amarin's amicus notes, "[c]ardiovascular disease is the leading killer of both men and women in the United States." Aimed Alliance Br. 16. JELIS thus provided a more lucrative reason to pursue the development of pure EPA.

Amarin is equally wrong to say obviousness "appears to go backwards" because Mori "pre-dates Lovaza®, first approved in the United States in 2004." Br. 36. While Lovaza was *approved* in 2004, it was *developed* much earlier. Testing on Lovaza (originally called Omacor) was first reported in 1997, three years before Mori. Appx88356. Amarin's argument that the makers of Lovaza ignored Mori is thus mistaken—Lovaza's development came first.

Amarin thus fails to show any error in the district court's secondary-considerations analysis—much less harmful error.

II. Amarin fails to show clear error in the district court's factual findings on motivation to combine and reasonable expectation of success.

Amarin concedes nearly all of the district court's findings as to prima-facie obviousness (and alleged unexpected results, Br. 34 n.6). Amarin does not dispute that "the only difference" between Lovaza PDR and the claimed method "is that Lovaza contained a mixture of EPA and DHA, instead of purified EPA." Appx57. Nor does it dispute that Lovaza raised LDL-C, and "a skilled artisan would have been motivated to develop a single pill that treats severe hypertriglyceridemia without LDL-C increases." *Id*. Thus, the only disputed issue is whether a skilled

artisan would reasonably expect pure EPA—which Amarin did not invent, and was available and used in Japan and in clinical studies—to achieve this goal. The district court found such "motivation to combine and reasonable expectation of success" as a matter of fact. Appx58. To be affirmed, factual findings only need to be "plausible in light of the entire record." *Kao*, 441 F.3d at 967. Here, the court's findings are not only "plausible," but strongly supported.

A. The record amply supports the court's finding that a skilled artisan would reasonably expect pure EPA to be LDL-neutral.

Amarin argues there is a "lack of evidence" supporting the court's reasonable-expectation-of-success finding. Br. 47. But the evidence that EPA would not increase LDL-C in severely hypertriglyceridemic patients was more than sufficient to support the court's finding. Amarin does not seriously dispute that at least three references, "Mori, Hayashi, and Kurabayashi[,] disclosed that EPA did not increase LDL-C." Appx58. Indeed, Amarin admits that in Hayashi, "EPA lowered triglycerides, but without an increase in LDL-C," and in Kurabayashi, both LDL-C and Apo B "went down significantly." Br. 16. Multiple prior-art studies reported the same results. *Supra* 9-11. Amarin does not cite a single reference suggesting otherwise.[3]

[3] At trial, Amarin relied on two papers that allegedly suggested an increase in LDL-C, but the court found them "not credible." Appx61; Appx30-32. Amarin does not dispute that finding, and any challenge to it is now waived.

Nevertheless, Amarin argues that "the court legally erred" in relying on these studies because they involved a different "patient population"—i.e., "those with *mild to moderately elevated triglycerides*" instead of "those with *severe hypertriglyceridemia*." Br. 47-48. Amarin's attempt to frame this issue as a "legal" argument lacks merit. Reasonable expectation of success is not a legal issue, but a "context-specific fact" reviewed for "clear error." *Acorda Therapeutics, Inc. v. Roxane Labs., Inc.*, 903 F.3d 1310, 1333-34 (Fed. Cir. 2018). "[T]o the extent that [Amarin]'s contention is a legal one, asserting a law-required minimum for what can support a 'reasonable' expectation of success, [Amarin] has offered no support for the contention." *Id*. at 1333.

This Court rejected a similar argument in *Persion*, where the patentee argued that the trial court "erred in its obviousness findings by relying on pharmacokinetic data from … patient groups not covered by the asserted claims." 945 F.3d at 1191. According to the patentee, a study on "hepatically unimpaired patients [wa]s irrelevant to motivation or expectation of success for administration of a drug to patients with hepatic impairment"—the claimed patient population. *Id*. at 1193. This Court disagreed, "find[ing] no clear error in the district court's crediting of expert testimony that relied on the [disputed] data." *Id*.

Here, too, the district court credited expert testimony by Dr. Heinecke relying on Mori, Hayashi, and Kurabayashi, which was not clearly erroneous. *E.g.*,

Appx25 (citing Appx1339(740:1-17)); Appx26-28 (citing Appx1324-1326(725:21-727:1); Appx28-30 (citing Appx1334(735:2-20), Appx1336(737:1-23)); Appx34 (citing Appx1314-1315(715:10-716:4), Appx1358-1359(759:10-760:1)).

Although these references did not specifically report LDL-C data for patients with triglycerides above 500mg/dL, they "taught that EPA did not increase LDL-C in patients with triglyceride levels up to 400 mg/dL." Appx34; Br. 16-17. Hayashi even broadly concluded, for a "phenotype [that] includes patients with severe hypertriglyceridemia," that EPA "has no deleterious effect on plasma LDL-C." Appx26-28; Appx88366-88367. And while 400 is numerically less than 500, the district court credited Dr. Heinecke's testimony that "there is no 'magical mechanistic difference' between having triglycerides of 400, 500, or 600 mg/dL." Appx61 (quoting Appx1395(796:5-20)). Indeed, "a patient could very easily have a triglyceride value of 400 or 450 one day and have a triglyceride value of 550 or 600 the next day." Appx1395(796:7-10). Moreover, pure EPA was commercially available in Japan since the early nineties, and multiple studies confirmed it was given to patients with triglycerides ≥500mg/dL (*supra* 11-12), yet there is no evidence pure EPA increased LDL-C in any patient in the prior art.

Whether Dr. Toth agreed with Dr. Heinecke is immaterial. In citing Dr. Toth's testimony throughout its brief, Amarin misunderstands this Court's role. Like most obviousness cases, this one turned on a battle of experts over scientific

issues. The district court heard from both sides and credited Dr. Heinecke over Dr. Toth. That "falls well within the wide discretion the court has to weigh expert credibility," to which "an appellate court defers." *Senju*, 780 F.3d at 1351.

Amarin's reliance on alleged "admissions" from Dr. Heinecke does not change the result. Amarin emphasizes Dr. Heinecke's statement that "somewhere above 500[mg/dL] the system for clearing triglycerides jams up." Br. 58. But this statement was not about LDL-C, or even how patients respond to triglyceride-lowering drugs. Rather, Dr. Heinecke was explaining the reason for the 500mg/dL threshold in the definition of severe hypertriglyceridemia—"[t]he concern with pancreatitis." Appx1395-1396(796:17-797:15). The district court found, and Amarin does not dispute, that "'the 500[mg/dL] threshold was not set because above 500 you are expected to have a greater increase in LDL-C.'" Appx60 (quoting Appx2654(1860:3-7) (Toth)). "Instead, all experts agreed that the threshold simply represents a marker for the risk of pancreatitis, which has nothing to do with LDL-C." Appx60-61.

Amarin insists "[i]t does not matter *why* the 500 mg/dL demarcation was set." Br. 57. But it *does* matter: As the district court recognized, the claims are broad enough to cover "patients with triglycerides of exactly 500 mg/dL." Appx58. Because "'claims which are broad enough to read on obvious subject matter are unpatentable even though they also read on nonobvious subject

matter,'" "Defendants do not need to prove that a skilled artisan would have reasonably expected success in achieving the claimed effects in patients with triglycerides above 500 mg/dL, much less substantially above that level." Appx58-59 (quoting *Cuozzo*, 793 F.3d at 1281). Amarin does not dispute this principle.

Amarin cannot show reversible error from Dr. Heinecke's statements that "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[mg/dL]," or "Hayashi is not telling us anything about the effect of EPA on LDL-C values in severely hypertriglyceridemic patients." Br. 48-49, 52. Dr. Heinecke was merely acknowledging the limitations of the "Friedewald equation" used in the prior art, which does not provide LDL-C data for patients with triglycerides above 400mg/dL. Appx1398-1399(799:17-800:5); Appx1493-1494(894:14-895:1). Of course, if data proving EPA's effects on severe hypertriglyceridemia were in the prior art, the claims would be more than just obvious—they would be anticipated. But "[c]onclusive proof of efficacy is not necessary to show obviousness. All that is required is a reasonable expectation of success." *Hoffmann-La Roche*, 748 F.3d at 1331.

Dr. Heinecke's testimony satisfies that standard. He confirmed a skilled artisan would have had "a reasonable expectation that EPA would not have LDL-C effects in patients above 500[mg/dL]." Appx1399(800:8-21). He further explained

that a skilled artisan would have relied on the prior-art data in patients with triglycerides below 500mg/dL, and would not "have expected a different result in patients above 500[mg/dL]." *Id.*; *accord* Appx1387-1388(788:25-789:22); Appx1509(910:8-17). The district court credited this testimony, recognizing that "even if … studies on patients with lower TGs did not provide 'conclusive proof' of EPA's effects, they were enough to form 'a reasonable expectation of success.'" Appx60 (quoting *Hoffmann*, 748 F.3d at 1331). Indeed, the prior art addressing pure EPA never suggested otherwise. The record thus supports the conclusion that skilled artisans "*can* draw reasonable inferences about the likelihood of success even without a perfectly designed clinical trial." *Acorda*, 903 F.3d at 1334.

Nor can Amarin rely on the lack of definitive proof in the prior art that EPA is LDL-neutral in severely hypertriglyceridemic patients. Amarin's own patents lack such proof. *Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364 (Fed. Cir. 2005), is on point. There, the patentee tried to distinguish prior art because it lacked data showing that the claimed method "overcame concerns in the art with adverse GI side effects." *Id*. at 1373. This Court disagreed because the asserted "patent sets forth no human clinical or laboratory data showing the safety and tolerability of the treatment methods," and "adds nothing beyond the [prior-art] teachings." *Id*. at 1374. So too here—even if there were "concerns in the art" about LDL-C effects in severely hypertriglyceridemic patients, Amarin's patents

recite no data to overcome such concerns. *Id*. at 1373-74; Appx2593-2595(1799:14-1801:11) (Toth); *Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1369 (Fed. Cir. 2012) (rejecting "argu[ment] that [prior art] would not give a skilled artisan an expectation" of safety because "neither does the … patent"); *Hoffmann*, 748 F.3d at 1331 (rejecting argument that prior art lacked "antifracture efficacy" data where the "patents do not themselves present [such] data").

Amarin's argument that skilled artisans would not rely on Mori is also belied by the fact that Mori was "repeatedly cited in … [Amarin's] internal documents and submissions to the FDA." Appx31; *supra* 13-16. Amarin says it did not rely on Mori as evidence of EPA's expected effects in severe hypertriglyceridemia patients (Br. 54), but the record shows otherwise. Amarin's statements were all in the context of the ">500 mg/dL population being targeted initially" for Vascepa's FDA approval. Appx90902; Appx90260. There was no reason to cite Mori unless its results applied to that population. In short, Amarin told FDA and its investors the precise opposite of what it now argues to this Court.

Nor do Amarin's prior statements about EPA's LDL-C effects follow "[t]he inventor's own path." Br. 55. None of these statements were made by named inventors, and none concern Amarin's own studies. They merely characterize the prior art. A court's "reliance on [a patentee's statements] merely as confirmation of how a [skilled artisan] would understand … prior art, is not erroneous." *In re*

Copaxone Consol. Cases, 906 F.3d 1013, 1030 (Fed. Cir. 2018); *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1365 (Fed. Cir. 2007) (relying on a "suggestion in [the patentee]'s supplemental filing with the FDA that it was known that the [invention] would work for its intended purpose").

The record thus supports the district court's factual findings and shows no clear error.

B. Amarin's evidence concerning the LDL-C effects of products *other* than EPA in patients with triglycerides *above* 500mg/dL is irrelevant and was properly discounted.

Amarin cites no prior-art teaching that EPA would raise LDL-C in any patients. Instead, Amarin relies on the effects of *different* products—Lovaza, fibrates, and niacin (Br. 7-12, 29)—to suggest that skilled artisans would believe that "patients with severe hypertriglyceridemia responded differently to triglyceride-lowering drugs … than those with milder hypertriglyceridemia." Br. 50, 48. But this is the same "factual premise" the district court rejected as "lack[ing] evidentiary support—that patients with TG levels above 500 mg/dL respond differently to TG-lowering therapy than patients with TG levels below 500 mg/dL." Appx60. Amarin shows no clear error in this finding.

Amarin mischaracterizes the record by saying "the district court found, and the experts agreed, [that] all prior art treatments for severe hypertriglyceridemia '*dramatically increase*[*d*] *LDL-C levels*.'" Br. 48 (quoting Appx5). But the

district court never said "all" previous treatments caused such increases, much less "in patients with triglycerides of exactly 500 mg/dL"—the relevant threshold "to prove obviousness." Appx58. Nor did the experts "agree" on this point, or concede that the effects of these treatments had any relevance to EPA.

To the contrary, the record shows that skilled artisans would not rely on evidence regarding Lovaza or other EPA-DHA mixtures to predict the effects of pure EPA. Dr. Toth admitted that EPA and DHA "clearly had some different effects," so "the fact that Lovaza itself has an LDL-C side effect doesn't answer the question of whether that side effect could be attributed to solely EPA." Appx2623(1829:6-8), Appx2595(1801:21-25). As the district court confirmed, "Mori concludes that 'EPA and DHA had differential effects on lipids,'" which "strongly suggest[s] that these two Omega-3 fatty acids could have distinct effects on LDL[-C].'" Appx25 (quoting Appx88480, Appx1339(740:1-17) (Heinecke)).

Amarin's evidence concerning fibrates and Lovaza also involved patients with triglycerides *above* 500mg/dL—726 and 816mg/dL. Appx108954-108955; Appx43940; Appx48910; Appx2611(1817:16-21), Appx2613-2615(1819:22-1821:2) (Toth). Again, however, the claims cover "patients with triglycerides of exactly 500 mg/dL," so whether LDL-C rises in patients with triglycerides "substantially above that level" is irrelevant. Appx58-59.

If anything, Amarin's fibrates data suggested that LDL-C would *not* increase at 500mg/dL. There was no significant increase in patients with triglycerides of 432mg/dL, which is closer to the 500mg/dL threshold than the data that Amarin relies on from patients with triglycerides of 726mg/dL. Appx108954. Indeed, Amarin admits that a "rise in LDL-C generally was not observed in patients with" triglycerides of "499 mg/dL" (Br. 8), which is "within error of the measurement" from 500mg/dL. Appx2614(1820:15-17) (Toth).

A skilled artisan also would not expect pure EPA to have the same effects as fibrates or niacin. Appx1400-1401(801:12-802:7), Appx1509-1511(910:21-912:17) (Heinecke). Dr. Toth "did not cite … any prior art comparing the LDL-C effects of niacin or fibrates on the one hand with pure EPA." Appx2598(1804:17-20). Likewise, during prosecution, "the examiner rejected Amarin's argument that a skilled artisan would extrapolate the results observed with a fibrate to omega-3 fatty acids like pure EPA" (Appx2598(1804:2-6)), which are "structurally and biologically very different." Appx88670.

Even if comparing EPA to other products made sense, there *were* triglyceride-lowering drugs in the prior art that did not raise LDL-C in severely hypertriglyceridemic patients. The 2007 label for Lipitor, a statin, reported reductions in both triglycerides *and* LDL-C in a clinical trial where the "median (min, max) baseline TG level was 565 (267-1502)"—i.e., a median of 565mg/dL,

ranging up to 1502mg/dL. Appx102640-102641; Appx94049. Because statins reduced triglycerides *without* raising LDL-C in severely hypertriglyceridemic patients, the court correctly rejected Amarin's premise that "[w]hatever the treatment, the results were the same." Br. 1; Appx1452(853:4-10), Appx1471-1472(872:17-873:18), Appx1509(910:8-17) (Heinecke); Appx2609-2611(1815:6-1817:8) (Toth).

Amarin acknowledges none of this, arguing instead that the court "ignored" its evidence by not expressly discussing "the differing effects of Lovaza® and fibrates in the two populations." Br. 28-29. But "the fact that the district court did not discuss" evidence "does not necessarily mean it was not considered." *Lab. Corp. of Am. Holdings v. Chiron Corp.*, 384 F.3d 1326, 1332 (Fed. Cir. 2004). Here the court *did* consider Amarin's alleged evidence and arguments, as shown by its citations to Amarin's post-trial brief. *E.g.*, Appx59-60 (citing "ECF No. 379" at 22-24 (Appx103390-103392)). Indeed, the court "note[d] that the parties made arguments … not discussed" in its opinion. Appx70. The court "reviewed these arguments" but "determined they do not materially affect the outcome of this case." *Id*. In arguing that the court "ignored … overwhelming evidence," Amarin overlooks that "the District Court had no obligation to write an opinion that reveals [its] assessment of every consideration." *Sarif Biomedical LLC v. Brainlab, Inc.*, 725 F. App'x 996, 1000 (Fed. Cir. 2018) (quotation omitted).

Regardless, even where a "court indeed provided little explicit support for its finding …, it is well established that, as an appellate tribunal, [this Court] review[s] judgments, not opinions." *Bruno Indep. Living Aids, Inc. v. Acorn Mobility Servs., Ltd.*, 394 F.3d 1348, 1354 (Fed. Cir. 2005). The question is "whether there is sufficient evidence in the record to sustain the judgment." *Id.* The detailed trial record here more than meets this standard.[4]

C. The district court did not "shift the burden" by rejecting Amarin's arguments and considering the prosecution history.

Unable to show clear error, Amarin tries to manufacture legal errors in the court's analysis. But Amarin shows no error, much less harmful error.

Amarin argues the court "shift[ed] the burden to Amarin" by finding "no reason to expect" different results in severe hypertriglyceridemia patients, and stating that "Dr. Toth cited no evidence" to the contrary. Br. 56. But Amarin is wrong. The district court understood that "Defendants … bear the ultimate burden of proving, by clear and convincing evidence, that the Asserted Claims are invalid." Appx55. That burden, however, "does not relieve the patentee of any responsibility to set forth evidence in opposition to a challenger's prima facie case which, if left unrebutted, would be sufficient to establish obviousness." *Novo*, 719 F.3d at 1353. While Amarin relied heavily on Dr. Toth's testimony to rebut

[4] At worst, the remedy for "ignoring" evidence would be remand—not reversal.

Defendants' evidence, the court properly found his testimony not credible because "Dr. Toth cited no evidence that the 500mg/dL threshold reflects any difference in how patients metabolize drugs, or any relationship between that specific threshold and LDL-C." Appx60. The court's "rejection of [Amarin]'s counterarguments" thus "does not constitute improper burden shifting." *Ignite*, 709 F. App'x at 1016; *Optivus Tech., Inc. v. Ion Beam Applications S.A.*, 469 F.3d 978, 991 (Fed. Cir. 2006) ("[T]he court's statement that 'there is no indication that the [invention] was non-obvious' …. in no way demonstrates a misallocation of the burden of proof").

Amarin argues that the "court's citation of the examiner's initial finding of obviousness that the applicants later overcame was also legal error." Br. 55. But Amarin does not articulate how a "citation" can be "legal error." Contrary to Amarin's argument, a "court should review the file history as part of its assessment of whether the invention claimed by the claims in suit are nonobvious." *Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1383 (Fed. Cir. 2005). Regardless, the court did not substitute the examiner's finding for proof of obviousness at trial. The court expressly found that "Defendants presented clear and convincing evidence *at Trial* that all Asserted Claims are invalid as obvious." Appx57 (emphasis added). And even if the court had found "a prima facie case of obviousness [solely] because the patent examiner initially rejected the claims" (which it did not), that would be "harmless error." *Pfizer*, 480 F.3d at 1359, 1361.

Amarin is also wrong in arguing that the court erred by assuming "Kurabayashi had not been cited to the patent office" and that the examiner "was not aware of Kurabayashi." Br. 30, 41. That is not what the court said. It found the "examiner did not *consider* Kurabayashi," which is true—Kurabayashi was never discussed in any office action. Appx66 (emphasis added). Because the examiner "did not expressly consider" Kurabayashi in any "specific PTO determination of nonobviousness," this Court should "reject [Amarin]'s deference-invoking argument." *Intercontinental*, 869 F.3d at 1350-51.

Lastly, Amarin insinuates the court erred by "cop[ying]" portions of Defendants' proposed findings. Br. 29, 57 n.8. But "[e]ven when a party drafts proposed findings of fact and conclusions of law, once adopted, the findings are those of the court and may be reversed only if clearly erroneous." *1st Media, LLC v. Elec. Arts, Inc.*, 694 F.3d 1367, 1372 (Fed. Cir. 2012) (quotation omitted). Because Amarin has shown no such error, this Court should affirm.

III. The record supports multiple alternative grounds for affirmance.

A. The seven claims that allow concurrent lipid therapy were also obvious because adding a statin was expected to achieve the claimed effects, and the remaining three claims are not infringed.

At a minimum, the seven asserted claims that permit concurrent lipid-altering therapy[5] were obvious for additional reasons the district court did not

[5] '677 claims 1 and 8, '652 claim 1, '560 claims 4 and 17, and '929 claims 1 and 5.

reach, and the three remaining claims that exclude concurrent lipid-altering therapy[6] are not infringed.

Obviousness. It was at least obvious to try administering pure EPA *with a statin* in a patient with severe hypertriglyceridemia, with a reasonable expectation of achieving all claimed effects—reducing triglycerides without increasing LDL-C, and reducing Apo B. Appx103363-Appx103366. This is true *even accepting* Amarin's (incorrect) argument that skilled artisans would not expect those effects with EPA alone. *Cuozzo*, 793 F.3d at 1281 (claims "read[ing] on obvious subject matter are unpatentable even though they also read on nonobvious subject matter").

It was undisputedly obvious to control LDL-C and Apo B with statins. As the district court found, "Lovaza PDR discloses clinical trials in which Lovaza was administered as … 'add-on therapy' to a statin"—given to patients "to control their LDL-C." Appx23 (citing Appx88409). "'[W]hen Lovaza is used with simvastatin, Apo B is decreased by 4.2 percent,'" and "the combination of Lovaza and simvastatin essentially caused 'zero' increase in LDL-C." *Id*. (quoting Appx2666-2667(1872:19-1873:2) (Toth)). As Amarin admits, "doctors frequently prescribed

[6] '728 claims 1 and 16, and '715 claim 14.

LDL-C lowering statins to their patients with severe hypertriglyceridemia." Br. 6; Appx24; Appx91708.

It was equally obvious to combine statins with pure EPA. As Dr. Toth admitted, "it was known that EPA could be used with a statin." Appx2670-2671(1876:25-1877:2). The Japanese study "JELIS involved pure EPA with a statin," which "motivated a skilled artisan to run a similar type of study in the United States." Appx2672-2673(1878:24-1879:1), Appx2697(1903:13-17) (Toth). And "pure EPA was given to at least one patient above 500 with a statin" in the prior art. Appx2672(1878:16-23) (Toth); Appx1332-1333(733:6-734:3) (Heinecke); Appx88490-88492 (Nakamura).

Dr. Toth conceded that a skilled artisan "would understand that if you give pure EPA with a statin," "you won't have as much of an LDL increase, or perhaps you won't increase LDL," and "you're likely to have an apo B decrease." Appx2673(1879:16-25). Dr. Toth admitted these results were expected regardless of "whether the triglyceride level is 400 or 550." Appx2674(1880:1-3). And as the court found, "a POSA 'would have reasonably expected purified EPA to reduce triglyceride levels above 500.'" Appx60 (quoting Appx2654(1860:12-15)).

Dr. Toth thus agreed it was "known in March 2008" that "pure EPA could be used with statins to reduce apo B and LDL-C" in the claimed population. Appx2675(1881:1-5). That "known" method reads on the seven claims that do not

exclude concurrent lipid-altering therapy, which "allow for the use of a statin … [to] not have an LDL-C increase" and "reduce apo B" in the claimed patient population. Appx2680(1886:6-24); *Gillette Co. v. Energizer Holdings, Inc.*, 405 F.3d 1367, 1371-72 (Fed. Cir. 2005) (transitional term "comprising" is "presumptively open ended" and "does not exclude additional, unrecited elements").

Noninfringement. The three remaining claims, which require that the patient "does not receive concurrent lipid altering therapy" (Appx10-11), are not infringed. Because Amarin asserted only method-of-treatment claims, and Defendants do not treat patients, Amarin did not assert direct infringement. Instead, it "asserted two indirect infringement theories"—inducement and contributory infringement under 35 U.S.C. §§ 271(b)-(c). Appx44 n.15. The court, however, "granted summary judgment to Defendants on Plaintiffs' contributory infringement theory," *id*., which Amarin did "not oppose" for claims that exclude concurrent lipid-altering therapy. Appx103434 n.6; Appx107365 n.17.[7] This is because Defendants' accused product labels state that "twenty-five percent of patients were on concomitant statin therapy" (a lipid-altering therapy) in Amarin's MARINE trial (Appx95783, Appx95828), which is undisputedly a

[7] Amarin has thus waived any challenge to the district court's finding of no contributory infringement for these claims.

"substantial noninfringing use" that precludes contributory infringement. 35 U.S.C. §271(c).

Although the court found infringement under Amarin's sole remaining theory—inducement—its factual findings do not satisfy the relevant legal standard. That standard requires proof that Defendants "have the specific intent, based on the contents of their proposed labels, to encourage physicians to use their proposed ANDA products" to infringe—i.e., "the label encourages, recommends, or promotes infringement." *Grunenthal GMBH v. Alkem Labs. Ltd.*, 919 F.3d 1333, 1339 (Fed. Cir. 2019). Because inducement in ANDA cases turns on the face of the "label in relation to the asserted claims," it can be decided "as a matter of law." *HZNP Meds. LLC v. Actavis Labs. UT, Inc.*, 940 F.3d 680, 699 (Fed. Cir. 2019) ("*Horizon*"). "The pertinent question is whether the proposed label instructs users to perform the patented method." *Grunenthal*, 919 F.3d at 1339 (quotation omitted). That "instruct[ion]" is especially critical where a "product has substantial noninfringing uses, and intent to induce infringement cannot be inferred." *Horizon*, 940 F.3d at 702 (quotation omitted).

Grunenthal and *Horizon* exemplify this principle. In *Grunenthal*, the accused drug was indicated for "severe chronic pain." 919 F.3d at 1339. This indication included, but was not limited to, the claimed method of treating "polyneuropathic pain." *Id*. The patentee argued the indication would inevitably

lead doctors to infringe. But this Court disagreed, holding that "even if severe chronic pain includes polyneuropathic pain, it also includes [other chronic] pain. Therefore, the proposed ANDA labels do not *specifically encourage* use of [the drug] for treatment of polyneuropathic pain." *Id*. (emphasis added).

Similarly, the claims in *Horizon* required a user to "(1) apply the inventive formulation, (2) wait for the area to dry, and (3) apply sunscreen, insect repellant, or a second topical medication." 940 F.3d at 702. The label described each claimed step—instructing users to "wait until the treated area is dry before applying a second topical agent." *Id*. at 686 (quotation omitted). But this Court found no inducement: "The patented method here *requires* three distinct steps," whereas the label "only *require*[*s*] the first step." *Id*. at 702 (emphasis added). Because "the label does not *require* subsequent application" of another agent, the label "does not encourage infringement." *Id*. (emphasis added).

Here, nothing in Defendants' labels "specifically encourages" or "requires" administering EPA without concurrent lipid-altering therapy. Instead of applying this legal standard, the district court mistakenly found it sufficient if the labels "suggest to doctors Defendants' proposed ANDA Products *could* be administered without a concurrent lipid altering therapy"—i.e., "*with or without* a statin or other lipid-lowering drug." Appx52 (emphasis added). The court thus found it significant that the labeling "does not contain any instructions that Defendants'

ANDA Products must be administered *with* a lipid-altering drug." *Id*. (emphasis added). At most, however, this merely confirms the approved use covers both monotherapy and combination therapy—neither is "specifically encourag[ed]." *Grunenthal*, 919 F.3d at 1339-40.

Mistakenly, the court wrote that "the Clinical Studies section … indicates that only 25% of the MARINE study participants were on a concomitant lipid-altering therapy." Appx53. From this alleged labeling statement, the court inferred that "[c]linicians appreciate … the remaining 75% of patients in the study described in the Clinical Studies section were not on concurrent lipid altering therapy." *Id*. But this was a mistake. The labels actually state that "twenty-five percent of patients were on concomitant *statin* therapy." Appx95783, Appx95828 (emphasis added). As Amarin's infringement expert, Dr. Budoff, admitted, "there are other lipid-altering therapies" besides statins, and "the labeling doesn't say anything about whether this 75 percent of patients were taking a different lipid-altering therapy." Appx1067(520:13-25), Appx1069(522:22-25).

Regardless, Dr. Budoff admitted the Clinical Studies section is "not mandating not to use a statin," and "there's nothing in the … label as a whole suggesting any preference for using [EPA] with or without a statin." Appx1069-1070(522:5-523:13). Instead, he agreed "defendants' labeling leaves it entirely up

to the physician's discretion as to whether to add a concurrent lipid-altering therapy to [EPA]." Appx1070(523:21-25). There is no inducement.

B. Defendants do not infringe any asserted claim because their labels do not induce doctors to administer EPA for at least 12 weeks.

Independently, Defendants do not infringe *any* asserted claim, all of which require administering EPA for at least 12 weeks. The district court dismissed Amarin's contributory infringement theory on this basis, finding "no real dispute" that "reducing triglycerides in less than 12 weeks using Defendants' ANDA drugs is a substantial non-infringing use." Appx103433-103434. Where, as here, a "product has substantial noninfringing uses, intent to induce infringement cannot be inferred." *Horizon*, 940 F.3d at 702 (quotation omitted).

Defendants' labels do not "specifically encourage" or "require" 12-week use, as *Grunenthal* and *Horizon* require. The district court acknowledged that no labeling instructions "explicitly tell doctors they should prescribe the drug for at least 12 weeks," and "prescribing Defendants' potential ANDA drugs for fewer than 12 weeks is within the scope of the FDA approval reflected in [the] labelling." Appx103430, Appx103433. Indeed, neither the "Indications and Usage" nor "Dosage and Administration" sections "specify any duration of use." Appx17-18. Thus, as Dr. Budoff admitted, the labels "leave it entirely up to the physician's discretion to determine the duration of treatment," and "it would be entirely consistent with defendants' labels for a doctor to prescribe icosapent for less than

12 weeks." Appx991-992(444:8-445:8). Likewise, Amarin's FDA expert, Dr. Peck, agreed "[t]he label is leaving it up to the discretion of the doctor as to the duration for a particular patient." Appx2095(1397:1-6). These admissions are dispositive, and none of the court's findings show otherwise.

First, the court found that patients need long-term therapy "in most cases," and "the drug will often be prescribed for long-term treatment." Appx47. But "proof that some, or even many, doctors would [infringe] is hardly evidence of" inducement. *Takeda Pharm. U.S.A., Inc. v. W.-Ward Pharm. Corp.*, 785 F.3d 625, 633 (Fed. Cir. 2015). That "a physician, without inducement by [Defendants], prescribes [EPA] in an infringing manner … is legally irrelevant." *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1364 (Fed. Cir. 2003). Such "infringement by others does not amount to inducement; specific intent and action to induce infringement must be proven." *Id*.

Second, the court found that "severe hypertriglyceridemia *generally* has a genetic component, meaning that it is *usually* a chronic condition." Appx47-48 (emphasis added). But the court also found "no real dispute that severe hypertriglyceridemia can be an acute condition some of the time." Appx48. Thus, as Dr. Peck admitted, "the indicated use of icosapent in defendants' labels is not limited to chronic use." Appx2059(1361:8-11). Under these facts, *Grunenthal*

precludes a finding of inducement because the indicated use does "not specifically encourage" infringement. 919 F.3d at 1339.

Whether doctors infringe "in most cases" is irrelevant. Appx48. That was also true in *Grunenthal*, where doctors used the drug for noninfringing conditions "less than 5%" of the time. *In re Depomed Patent Litig.*, 2016 WL 7163647, *69 (D.N.J. Sept. 30, 2016), *aff'd sub nom. Grunenthal*, 919 F.3d 1333. Likewise, Dr. Budoff "treated patients with Vascepa for less than 12 weeks about 5% of the time, which is consistent with [the] labelling." Appx103433; Appx1048(501:11-14).

Third, the court cited "the Clinical Studies section," which "states that patients were administered icosapent ethyl 4 g per day 'for 12 weeks.'" Appx48; Appx95783; Appx95828. But as the court acknowledged, this does not "explicitly tell doctors they should prescribe the drug for at least 12 weeks"—it merely "*describes* a clinical trial … in which patients were enrolled for 12 weeks." Appx103430 (emphasis added). "Merely describing the infringing use … will not suffice." *Horizon*, 940 F.3d at 702. As Dr. Peck agreed, "the labeling is telling doctors that they *can* use the drug for 12 weeks or longer if they want, but it's not saying that they *should*." Appx2095(1397:1-6) (emphasis added).

Thus, regardless of Amarin's arguments against obviousness, the Court should affirm because Defendants do not infringe any asserted claim.

C. Alternatively, all asserted claims lack written description.

Finally, even if the Court were to find the asserted claims nonobvious because the prior art provided no reasonable expectation of success, the claims would be invalid under 35 U.S.C. §112 for lacking written description. Again, Amarin's patents contain no data or evidence that EPA achieves the claimed effects. Appx73-207; Appx2593-2595(1799:11-1801:11) (Toth). Thus, if skilled artisans lacked a reasonable expectation of success from the prior art, they also would not believe based on the specification that Amarin's inventors possessed the claimed methods when Amarin filed its patent application.

Nuvo Pharmaceuticals (Ireland) Designated Activity Co. v. Dr. Reddy's Labs. Inc., 923 F.3d 1368 (Fed. Cir. 2019), is instructive. The Court there found "that none of the asserted claims are obvious over the prior art" because skilled artisans "would not have reasonably expected [the claimed method] to work." *Id.* at 1374-75. As a result, however, the claims lacked written description because "the specification … does not provide any data showing that [the claimed drug] is effective." *Id.* at 1382. Likewise, if this Court "found upon [Amarin's] insistence as part of its obviousness analysis that ordinarily skilled artisans would not have expected" EPA to lower triglycerides and Apo B without raising LDL-C, the claims would be invalid because "the specification … does not provide any data showing" those results. *Id.* at 1377, 1382.

On summary judgment, the district court dismissed this alternative defense solely because Defendants "did not indicate they intended to assert a written description defense in their opening expert report." Appx103439. But Defendants never intended to present this alternative defense through their own expert. Defendants raised it as a legal matter only in the event the court accepted *Amarin's* expert testimony on the state of the art. Appx106554-106560.

Regardless, there is no legal requirement for expert testimony to preserve a written-description defense. Patents "can be held invalid for failure to meet the written description requirement, based solely on the language of the patent specification. After all, it is in the patent specification where the written description requirement must be met." *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927 (Fed. Cir. 2004). The "argu[ment] that [Defendants] failed to present any expert testimony" on written description thus fails, because "there is no strict requirement for extrinsic evidence (expert or otherwise) … [to] determine whether the written description requirement has been satisfied." *Adang v. Umbeck*, 2007 WL 3120323, *2 (Fed. Cir. Oct. 25, 2007).

Again, the Court need not reach this (or any other) alternative ground, because the district court did not commit any error in finding a reasonable expectation of success. If any such error existed, however, all asserted claims

would lack written description because there is no evidence in the specification that Amarin "invented" anything when it filed its patents.

CONCLUSION

The judgment should be affirmed.

Respectfully submitted,

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June 16, 2020

CERTIFICATE OF SERVICE

I certify that true and correct copies of the foregoing *Brief for Defendants-Appellees* were caused to be served on June 16, 2020, on all counsel of record by the CM/ECF system.

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