IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

IN RE ENTRESTO (SACUBITRIL/VALSARTAN) PATENT LITIGATION	MDL No. 20-2930-RGA
NOVARTIS PHARMACEUTICALS CORPORATION, Plaintiff, v. AUROBINDO PHARMA USA INC., AUROBINDO PHARMA LTD., CRYSTAL PHARMACEUTICAL (SUZHOU) CO., LTD., TORRENT PHARMA INC., TORRENT PHARMACEUTICALS LTD., Defendants.	C.A. No. 19-1979-RGA
NOVARTIS PHARMACEUTICALS CORPORATION, Plaintiff, v. ALEMBIC PHARMACEUTICALS LIMITED, ALEMBIC GLOBAL HOLDING SA, ALEMBIC PHARMACEUTICALS, INC., MACLEODS PHARMACEUTICALS LTD., MACLEODS PHARMA USA, INC., Defendants.	C.A. No. 19-2021-RGA

NOVARTIS PHARMACEUTICALS CORPORATION, Plaintiff, v. DR. REDDY'S LABORATORIES, INC., DR. REDDY'S LABORATORIES, LTD., HETERO USA INC., HETERO LABS LIMITED, HETERO LABS LIMITED UNIT III, MSN PHARMACEUTICALS INC., MSN LABORATORIES PRIVATE LIMITED, MSN LIFE SCIENCES PRIVATE LIMITED, NOVUGEN PHARMA (MALAYSIA) SDN. BHD., Defendants.	C.A. No. 19-2053-RGA

NOVARTIS'S POST-TRIAL ANSWERING BRIEF ON THE VALIDITY OF THE '659 PATENT

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Cases

TABLE OF ABBREVIATIONS

'217 patent	U.S. Patent No. 6,211,217 (DTX 686)
'331 patent	U.S. Patent No. 8,796,331 (JTX 3)
'578 patent	U.S. Patent No. 5,399,578 (JTX 23)
'659 patent	U.S. Patent No. 8,101,659 (JTX 1)
'996 patent	U.S. Patent No. 5,217,996 (JTX 362)
Aakeröy 1997	Aakeröy, "Crystal Engineering: Strategies and Architectures," Acta Cryst. (1997) B53:569–586 (JTX 254)
ACE	angiotensin converting enzyme
Almarsson 2004	Almarsson & Zaworotko, "Crystal engineering of the composition of pharmaceutical phases. Do pharmaceutical co-crystals represent a new path to improved medicines?," Chem. Commun. (2004) 17:1889–1896 (JTX 234)
ARB	angiotensin receptor blocker
BMS	Bristol-Myers Squibb
Cleland	Cleland & Swedberg, "Lack of efficacy of neutral endopeptidase inhibitor ecadotril in heart failure," Lancet (1998) 351:1657–1658 (JTX 56)
Cohn	Cohn & Tognoni, "A Randomized Trial of the Angiotensin-Receptor Blocker Valsartan in Chronic Heart Failure," New Engl. J. Med. (2001) 345(23):1667–1675 (JTX 60)
CYP17	Cytochrome P450, family 17
CYP450	Cytochrome P450
Defendants	The Crystal, Dr. Reddy's, Hetero, Macleods, MSN, and Torrent defendants
Defs' Disputed Facts	Joint Pretrial Order Exh. 3 Defendants' Statement of Disputed Facts (C.A. 20-md-02930-RGA, D.I. 737)
DFoF	Defendants' Post-Trial Proposed Findings of Fact Regarding The '659 Patent (C.A. 20-md-02930-RGA, D.I. 889)
Diovan® Label	Physicians' Desk Reference (53rd Ed. 1999), pages 2013–2015 (Entry for Diovan®) (JTX 67)
Diovan® PDR	Physicians' Desk Reference (55th Ed. 2001), pages 2166–2168 (Entry for Diovan®) (PTX 189)
EP '072	European Patent Application No. 726,072 (JTX 368)
FDA	Food and Drug Administration
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
Ksander	Ksander et al., "Dicarboxylic Acid Dipeptide Neutral Endopeptidase Inhibitors," J. Med. Chem. (1995) 38:1689–1700 (JTX 352)
LVEDP	left ventricular end diastolic pressure
LVEF	left ventricular ejection fraction
LVSP	left ventricular systolic pressure
Malacco	Malacco et al., "Comparison of Valsartan and Irbesartan in the Treatment of Mild to Moderate Hypertension: A Randomized, Open-

	Label, Crossover Study," Curr. Therapeutic Res. (2000) 61(11):789–797 (JTX 118)
Mann 2020	Mann et al., "Sacubitril/Valsartan in Advanced Heart Failure With Reduced Ejection Fraction," J. Am. Coll. Cardiol. (2020) 8(10):789–799 (JTX 212)
Mann 2022	Mann et al., "Effect of Treatment With Sacubitril/Valsartan in Patients With Advanced Heart Failure and Reduced Ejection Fraction," J. Am. Med. Ass'n Cardiol. (2022) 7(1):17–25 (JTX 213)
McMurray	McMurray et al., "Angiotensin-Neprilysin Inhibition versus Enalapril in Heart Failure," New Engl. J. Med. (2014) 371(11):993–1004 (JTX 129)
Morissette 2004	Morissette et al., "High-throughput crystallization: polymorphs, salts, co-crystals and solvates of pharmaceutical solids," Adv. Drug Del. Rev. (2004) 56:275–300 (JTX 252)
NEP	neutral endopeptidase
Ngilirabanga 2021	Ngilirabanga & Samsodien, "Pharmaceutical co-crystal: An alternative strategy for enhanced physicochemical properties and drug synergy," Nano Select (2021) 2:512–526 (JTX 240)
Novartis	Novartis Pharmaceuticals Corporation
Op. Br.	Defendants' Post-Trial Brief Regarding The '659 Patent (C.A. 20-md-02930-RGA, D.I. 888)
PFoF	Novartis's Proposed Findings of Fact Regarding The '659 Patent
POSA	person of ordinary skill in the art
Shetty	Shetty & DelGrande, "Differential Inhibition of the Prejunctional Actions of Angiotensin II in Rat Atria by Valsartan, Irbesartan, Eprosartan, and Losartan," J. Pharmacol. & Exper. Therapeutics (2000) 294(1):179–186 (JTX 169)
Solomon 2019	Solomon et al., "Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction," New Engl. J. Med. (2019) 381(17):1609–1620 (JTX 178)
Solomon 2020	Solomon et al., "Sacubitril/Valsartan Across the Spectrum of Ejection Fraction in Heart Failure," Circulation (2020) 141:352–361 (JTX 179)
SQ 28603	NEP inhibitor from Trippodo/EP '072
Taavitsainen	Taavitsainen et al., "In vitro inhibition screening of human hepatic P_{450} enzymes by five angiotensin-II receptor antagonists," Eur. J. Clin. Pharmacol. (2000) 56:135–140 (JTX 218)
Tr.	Transcript of the September 12-14, 2022 Trial (C.A. 20-md-02930-RGA, D.I. 882, 883, and 884)
Trippodo	Trippodo et al., "Repression of Angiotensin II and Potentiation of Bradykinin Contribute to the Synergistic Effects of Dual Metalloprotease Inhibition in Heart Failure," J. Pharmacol. & Exper. Therapeutics (1995) 272(2):619–627 (JTX 369)
Uncontested Facts	Joint Pretrial Order Exh. 1 Joint Statement of Uncontested Facts (C.A. 20-md-02930-RGA, D.I. 737)
USPTO	United States Patent and Trademark Office

I. INTRODUCTION

Entresto® is a breakthrough therapy for chronic heart failure. Entresto® is covered by the '659 patent, which claims combinations of the ARB valsartan and the NEP inhibitor sacubitril in an about 1:1 weight ratio. Defendants stipulated to infringement of the '659 patent claims, Uncontested Facts ¶ 12, but assert the claims are invalid.[1]

The '659 patent is presumed valid. 35 U.S.C. § 282. Defendants have not met their burden to present clear and convincing evidence on any of their four theories for why the asserted claims of the '659 patent are invalid — obviousness, enablement, written description, or indefiniteness.

As to obviousness, Defendants begin their analysis in the middle, with a POSA already having decided to use an ARB/NEP inhibitor combination, ignoring the many hypertension and heart failure drugs and drug classes available as of the January 17, 2002 ("2002") priority date. That is classic hindsight. Worse still, Defendants' primary prior art—Trippodo and EP '072, the only cited prior art with ARB/NEP inhibitor combination data—taught that an ARB/NEP inhibitor combination failed to lower blood pressure and was apt to worsen heart failure. In the face of the negative Trippodo/EP '072 data, Defendants use further hindsight to pick a second starting point (an ACE/NEP inhibitor combination) and offer two theoretical motivations to substitute an ARB for the ACE inhibitor component, but Defendants fail to corroborate those theories with evidence. Again, the only ARB/NEP inhibitor data Defendants cite would have discouraged a POSA from pursuing such a combination.

Even if a POSA had decided to pursue an ARB/NEP inhibitor combination, Defendants

[1] At trial, Defendants also asserted the '331 patent is invalid. But the parties have since agreed the Court need not reach a decision regarding the validity of the '331 patent and Defendants agreed not to launch their respective ANDA Products until after the expiration of the '331 patent and period of pediatric exclusivity. C.A. No. 20-2930, D.I. 886.

fail to provide clear and convincing evidence that a POSA would have been motivated to select valsartan and sacubitril specifically. As of 2002, the NEP inhibitor sacubitril had never been administered to humans, much less studied in hypertension or heart failure animal models. The potency, selectivity, and drug-drug interaction characteristics Defendants tout as reasons to choose the ARB valsartan were all undermined by the very art they cited. Defendants assert a POSA would have been motivated to replace the ARB irbesartan with valsartan, but it was undisputed that irbesartan was a better anti-hypertensive than valsartan.

The objective evidence of nonobviousness confirms Defendants' hindsight. For example, multiple industry leaders identified Entresto® (sacubitril/valsartan) tablets' heart failure benefits as substantial. Defendants' rebuttals are legally or factually wrong. Indeed, Defendants' expert Dr. Fintel admitted Entresto® is a very good drug, he increasingly prescribes it, and agreed it was better than the previous standard of care in improving the key heart failure endpoints. The objective evidence highlights the lack of clear and convincing evidence of obviousness.

As to enablement, Defendants and their expert Dr. Steed have not disputed that the '659 patent enables combinations of valsartan and sacubitril where valsartan and sacubitril are present as separate components in a physical mixture. The issue for this Court is whether the '659 patent was also required to enable a combination of valsartan and sacubitril in the form of a non-covalently bound complex ("complex"). Under *Hogan* and its Federal Circuit progeny (*Chiron* and *U.S. Steel*), the '659 patent was not required to enable these after-arising embodiments, and Defendants have failed to show lack of enablement by clear and convincing evidence.

As to written description, Defendants and their expert Dr. Steed likewise have not disputed the '659 patent discloses, in structural terms, the claimed combination of valsartan and sacubitril. The '659 patent thereby satisfies the written description requirement under *Ariad*'s common

structural features test by disclosing the structural features common to the members of the claimed genus: the pharmaceutical composition containing the combination of valsartan and sacubitril. Defendants have not met their clear and convincing evidence burden on written description.

Finally, the '659 patent claims clearly inform a POSA that the claimed ratio refers to a weight ratio, and is not indefinite, in view of repeated and consistent references to weight amounts and dosages in the specification and file history. Defendants' conclusory indefiniteness allegations mentioned only in a footnote are not clear and convincing evidence.

II. DEFENDANTS HAVE FAILED TO PROVE OBVIOUSNESS

Defendants asserted that the '659 patent claims are obvious because a POSA "would have been motivated to combine [the ARB] valsartan and [the NEP inhibitor] sacubitril, and had a reasonable expectation of success that this combination would be effective to treat either hypertension or heart failure." PFoF ¶ 8 (citing Tr. 45:2–8 (Fintel)). But since a POSA would not have reasonably expected that combining valsartan and sacubitril would treat hypertension or heart failure, he or she would not have been motivated to combine them in the first place. PFoF ¶ 22. *See Intelligent Bio-Systems, Inc. v. Illumina Cambridge, Ltd.*, 821 F.3d 1359, 1368 (Fed. Cir. 2016) (finding that a lack of reasonable expectation of quantitative deblocking "is irrelevant to a finding that there was no reasonable expectation of success in meeting the claims . . . , which do not require quantitative deblocking at all, it is central to a finding of no motivation to combine. This is because the petitioner's *sole* argument for why one of skill in the art would be motivated to combine" two references was to achieve "quantitative deblocking"); *DePuy Spine v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) ("An inference of nonobviousness is especially strong where the prior art's teachings undermine the very reason being proffered as to why a person of ordinary skill would have combined the known elements.").

A. EP '072/Trippodo Would Have Discouraged a POSA From Combining an ARB and a NEP Inhibitor

The only prior art ARB/NEP inhibitor combination Defendants cited was SQ 28603/ irbesartan disclosed in EP '072 and Trippodo. PFoF ¶¶ 23–24, 27–28, 33–34. Those references disclose data for that combination in a hypertension animal model (EP '072, Example 2 – the 1K1C dog) and a heart failure animal model (Trippodo/EP '072, Example 1 – the cardiomyopathic hamster). PFoF ¶¶ 24, 27, 33; JTX 368 (EP '072); JTX 369 (Trippodo). Defendants failed to show that either data set would have motivated a POSA to combine an ARB and a NEP inhibitor, or valsartan and sacubitril specifically, to treat hypertension or heart failure. Rather, the data would have discouraged an ARB/NEP inhibitor combination. PFoF ¶¶ 30, 32, 35.

1. *A POSA Would Have Concluded the ARB/NEP Inhibitor Combination Had No Antihypertensive Effect*

First, a POSA would have concluded that the ARB/NEP inhibitor combination disclosed in EP '072/Trippodo failed to lower arterial blood pressure (*i.e.*, treat hypertension), much less synergistically. PFoF ¶¶ 34–36. That conclusion is based on four facts—all four of which both sides' experts agreed on. First, the only hypertension model disclosed in EP '072 (or disclosed in the prior art at all) was the 1K1C dog model of Example 2. PFoF ¶¶ 24, 33, 38. Second, in that hypertension model, the ARB/NEP inhibitor combination had no antihypertensive effect. PFoF ¶ 35. Third, to know if a combination lowers blood pressure, a POSA would need to test it in a hypertension model (*e.g.*, the model of Ex. 2). PFoF ¶ 38. Fourth, the cardiomyopathic hamster model is not a model of hypertension (*i.e.*, the left ventricular pressure data (LVEDP and LVSP) disclosed in EP '072 (Ex. 1)/Trippodo is not from a hypertension model). PFoF ¶¶ 27–28, 40.

Admitting he does not have expertise in hypertension models, PFoF ¶ 25, and inconsistent with the four above agreed-upon facts, Dr. Fintel still concluded that LVEDP and LVSP reductions

were sufficient to demonstrate that the ARB/NEP inhibitor combination had a hypertensive effect. DFoF ¶ 49. Dr. Fintel testified that lowering LVSP treats hypertension because LVSP is generally the same as systolic blood pressure. DFoF ¶ 42. But Dr. Spinale (who, unlike Dr. Fintel, is an expert in hypertension and heart failure animal models) explained why Dr. Fintel's conclusion was wrong. PFoF ¶¶ 39–42. EP '072 (Ex. 1)/Trippodo measured *peak* LVSP, which is not the same as or a surrogate measure of systolic blood pressure. PFoF ¶ 42. Defendants' response is that if a POSA were to ignore the EP '072 hypertension experiment's negative results (Ex. 2) and focus only on the heart failure experiment (Ex. 1), the POSA would have found the heart failure experiment encouraging for hypertension. Op. Br. at 7. Of course, Defendants cannot "pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." *In re Wesslau*, 353 F.2d 238, 241 (C.C.P.A. 1965); *Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1332 (Fed. Cir. 2019) (applying the "longstanding principle that the prior art must be considered for all its teachings, not selectively").

That legal error aside, a POSA would not consider heart failure data relevant to treating hypertension. PFoF ¶ 11. They are different conditions: hypertension is a disease of the arteries, and heart failure is a disease of the heart muscle. PFoF ¶ 12. As of 2002, researchers used different methods to study each condition. PFoF ¶ 13. Physicians had different goals and guidelines in treating hypertension and heart failure. PFoF ¶ 14. And there were drugs used to treat hypertension that were not used to treat (and even dangerous for) heart failure, and vice versa. PFoF ¶ 15.

To justify blurring the line between hypertension and heart failure, Defendants assert (i) hypertension can precede the development of heart failure, and (ii) controlling blood pressure could prevent some of hypertension's severe consequences, including the development of heart

failure. Op. Br. at 5. Even if correct, neither is relevant to the motivation that Defendants assert a POSA would have had: relying on the EP '072 heart failure model as a motivation to use the combination to treat hypertension. *See* Op. Br. at 7, 10. Treating hypertension is different than treating heart failure, treating heart failure is different than treating hypertension, and Defendants do not assert otherwise. Regardless, Dr. Fintel still admitted that to answer the question of whether a combination treats hypertension, a POSA would need to test it in a hypertension model. PFoF ¶ 38. When so tested, the ARB/NEP inhibitor combination did not lower blood pressure in a hypertension model. PFoF ¶ 38.

2. *A POSA Would Have Concluded the ARB/NEP Inhibitor Combination Would Worsen, Not Treat, Heart Failure*

Second, a POSA would have concluded that the ARB/NEP inhibitor combination was apt to worsen heart failure, not treat it, much less synergistically. PFoF ¶¶ 30–31. There is no dispute that the cardiomyopathic hamster model disclosed in Trippodo and EP '072 Example 1 is a model of heart failure. PFoF ¶ 27. And there is no dispute that there was a large, abrupt drop in LVSP. PFoF ¶ 30. Backed by scientific literature, Dr. Spinale explained that a POSA would have concluded that the LVSP data portends a worsening of heart function. PFoF ¶¶ 30–31. Thus, while the reduction in LVEDP is beneficial in isolation, when considered together with the reduction in LVSP, a POSA would have recognized that this was not a synergistic treatment effect. PFoF ¶ 32. Dr. Fintel offered conclusory disagreement, but he is neither an expert in heart failure animal models, nor did he offer any reasoning or independent support for his disagreement. PFoF ¶ 25.

3. *The Real-World Facts Corroborate That a POSA Would Have Viewed the Trippodo/EP '072 Data Negatively*

Finally, Defendants brush off the red flags in Trippodo and EP '072 as "quibble[s]" with the data and at odds with the conclusion drawn in EP '072 by the patent applicant (BMS). Op. Br.

at 1. But this ignores how a POSA would have viewed EP '072 in the context of the prior art as a whole, and there is no scientific reason or legal requirement that the Court accept a prior art statement when the weight of the data is against the statement. *In re Bell*, 991 F.2d 781, 785 (Fed. Cir. 1993) (explaining that "a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests" and refusing to take at face value a reference's express disclosure that its method could be "easily" applied because the reference as a whole would not fairly suggest that to a POSA). Prior to 2002, BMS abandoned EP '072, and neither BMS nor anyone else clinically developed an ARB/NEP inhibitor combination—evidence that the data was problematic. PFoF ¶¶ 43–46. Thus, considering the data and the real-world facts together, Defendants have failed to prove that Trippodo/EP '072—the only ARB/NEP inhibitor disclosure cited—would have motivated a POSA to combine an ARB and a NEP inhibitor to treat hypertension or heart failure, much less valsartan and sacubitril specifically.

B. A POSA Would Not Have Been Motivated to Replace the ACE Inhibitor in an ACE/NEP Inhibitor Combination

The evidence does not support Defendants' assertions that a POSA would have substituted an ARB for the ACE inhibitor component of an ACE/NEP inhibitor combination. Even if there were theoretical reasons to use an ARB in place of an ACE inhibitor in an ACE/NEP inhibitor combination, a POSA would have been discouraged by the actual data disclosed in Trippodo/EP '072. *Supra* § II.A. The real world facts indeed demonstrate that no one pursued clinical development of an ARB/NEP inhibitor combination. PFoF ¶¶ 43–46. Thus, "the prior art's teachings undermine the very reason" that Defendants proffer "as to why a person of ordinary skill would have combined" an ARB and a NEP inhibitor, namely an expectation of improved efficacy or reduced side effects. *DePuy Spine*, 567 F.3d at 1326.

1. *A POSA Would Not Have Been Motivated to Use an ARB, Including in Combination with a NEP Inhibitor, to Address ACE Inhibitor-Associated Side Effects*

As of 2002, ACE inhibitors were the standard of care for treating hypertension and heart failure. PFoF ¶ 76; Tr. 312:20–24 (Spinale). Omapatrilat – a molecule that inhibited ACE and NEP – was in clinical development for treating hypertension and heart failure. PFoF ¶¶ 47, 82. Defendants argue that ACE inhibitors and omapatrilat increased bradykinin, which in turn led to angioedema. Op. Br. at 6. Defendants rely on bradykinin-induced angioedema ostensibly as motivation to use an ARB in place of an ACE inhibitor (or in place of the ACE inhibitor component of an ACE/NEP inhibitor like omapatrilat). Op. Br. at 7–8. But there are at least four problems with Defendants' bradykinin-induced angioedema motivation.

First, ACE inhibitors and omapatrilat were well-tolerated, and the incidence of angioedema was very low. PFoF ¶¶ 76, 82–83. The data (*i.e.*, closest to January 2002) showed that the rate of angioedema with omapatrilat was similar to ACE inhibitors (the standard of care). PFoF ¶¶ 76, 83. And BMS continued developing omapatrilat up to and through January 2002, providing real world evidence that undercuts Defendants alleged motivation to modify omapatrilat. PFoF ¶ 82.

Second, even assuming ACE inhibitor side effects were a problem in need of solving, the evidence does not point to an ARB/NEP inhibitor as a solution. ARBs, like ACE inhibitors, were associated with angioedema, and Dr. Fintel was wrong to say otherwise. PFoF ¶ 79. The 2001 Diovan® (valsartan) label directly contradicts his testimony, as it lists angioedema as a side effect of this ARB. PFoF ¶ 79; PTX 189 (Diovan® PDR) at 2167. And the prior art expressly cautioned against substituting an ARB for an ACE inhibitor in patients with angioedema. PFoF ¶ 80.

Third, as of 2002, it was not known what caused angioedema. PFoF ¶ 77. Dr. Fintel blamed bradykinin, yet he offered no prior art evidence in support (referencing only a YouTube video that

he did not create, did not verify the date of, and which was not offered into evidence). Tr. 124:14–125:13. *See Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 294 (Fed. Cir. 1985) ("Lack of factual support for expert opinion going to factual determinations . . . may render the testimony of little probative value in a validity determination."); *see also ATEN Int'l Co., Ltd. v. Uniclass Tech. Co., Ltd.*, 932 F.3d 1364, 1368 (Fed. Cir. 2019) (explaining that the burden is on the patent challenger to prove by clear and convincing evidence that a reference is prior art). Since it was not known whether bradykinin caused angioedema, a POSA would not have known whether a drug that did not potentiate bradykinin (like an ARB) would avoid angioedema. PFoF ¶ 77.

Fourth, even assuming bradykinin was a cause of angioedema, a combination that included a NEP inhibitor would not have solved the problem, because NEP inhibition also potentiates bradykinin, causing the same side effects Defendants allege were associated with ACE inhibitors and omapatrilat. PFoF ¶¶ 81, 83. Thus, Defendants have not clearly and convincingly proved a POSA would have been motivated to address ACE inhibitor side effects by using an ARB in place of an ACE inhibitor (or in place of the ACE inhibitor component of an ACE/NEP inhibitor).

2. *A POSA Would Not Have Been Motivated to Use an ARB with a NEP Inhibitor to Counteract an Increase in Angiotensin II*

The prior art does not suggest that a POSA could have combined an ARB with a NEP inhibitor to unmask the benefits of the NEP inhibitor. *Contra* Op. Br. at 7–8. Defendants' theory is that NEP inhibitors have beneficial effects but also increase angiotensin II (a substance associated with negative cardiovascular effects), and so combining a NEP inhibitor with a drug that blocks angiotensin II (an ARB) would unmask the benefits of NEP inhibitors. *Id.* Defendants cite no prior art that suggested such a motivation (Cleland certainly does not), and so the theory is of little probative value in meeting Defendants' burden to prove a motivation to combine valsartan and sacubitril by clear and convincing evidence. *See Ashland Oil, Inc.*, 776 F.2d at 294. And in

fact, the prior art showed that NEP inhibition did not increase angiotensin II; rather NEP inhibition did not change or likely decreased angiotensin II. PFoF ¶ 20; *see Purdue Pharma L.P. v. Depomed, Inc.*, 643 F. App'x 960, 966 (Fed. Cir. 2016) (affirming nonobviousness where challenger "relie[ed] on the problem to be solved to supply the reason to combine the prior art, [but] failed to demonstrate . . . the problem was known in the art or that [the challenger's] formulation of the problem was derived directly from the prior art, rather than from the challenged claims."). Thus, a POSA would not have been motivated to use an ARB with a NEP inhibitor to counteract an increase in angiotensin II because no such increase would have been expected. PFoF ¶ 20.

C. No Motivation to Combine an ARB and a NEP Inhibitor Just Because Other Combinations Had Been Used to Treat Hypertension or Heart Failure

A POSA would not have reasonably expected that combining drugs from different classes would successfully and safely treat hypertension or heart failure. PFoF ¶¶ 18–19. Even drugs previously known for treating heart failure could be detrimental when combined for that indication. PFoF ¶¶ 15, 18. Indeed, Dr. Fintel admitted that drugs with complementary mechanisms can interact in a detrimental way. PFoF ¶ 18. To find out, a POSA would have to test the combination. PFoF ¶ 18. And when tested by BMS in the mid-1990s, an ARB/NEP inhibitor combination failed to lower blood pressure in a hypertension model and its results in a heart failure model suggested a detrimental effect. *Supra* § II.A (discussing EP '072/Trippodo). As of 2002, BMS's data was the only data available for an ARB/NEP inhibitor combination. PFoF ¶¶ 27, 38. Thus, Defendants failed to prove by clear and convincing evidence that a POSA would have been motivated to combine an ARB and a NEP inhibitor (much less valsartan and sacubitril specifically), just because other combinations had been used to treat hypertension or heart failure, especially in view of the large number of hypertension and heart failure drugs and drug classes known as of 2002. PFoF ¶¶

9, 16–19; *contra* Op. Br. at 1, 10, 13.

Defendants are incorrect that, as a matter of law "[a] motivation to combine exists where two drugs are disclosed to treat the same condition" or "a reasonable expectation exists for combining two drugs having the same indications." *Id.* at 3 (citing *Nalpropion v. Actavis* and *BTG v. Amneal*). *See, e.g.*, *Sanofi-Aventis Deutschland GmbH v. Glenmark Pharm., Inc.*, 748 F.3d 1354, 1358–61 (Fed. Cir. 2014) (affirming combination of two antihypertensive drugs was not obvious). Obviousness "is highly fact-specific and not susceptible to per se rules." *Litton Sys., Inc. v. Honeywell, Inc.*, 87 F.3d 1559, 1567 (Fed. Cir. 1996), vacated on other grounds, 520 U.S. 1111 (1997). Motivation to combine valsartan and sacubitril to treat hypertension or heart failure and reasonable expectation of success are findings of fact that Defendants must prove by clear and convincing evidence. *In re Cyclobenzaprine*, 676 F.3d 1063, 1068–69 (Fed. Cir. 2012).

The facts here are also different from the drug combination cases on which Defendants rely. In *Nalpropion*, combining naltrexone and bupropion for treating obesity was obvious because (i) the prior art combined naltrexone and bupropion (*i.e.*, the exact drugs claimed) to minimize weight gain; (ii) naltrexone caused weight loss in clinical trials; and (iii) bupropion caused weight loss in clinical trials. *Nalpropion Pharm., Inc. v. Actavis Lab'ys FL, Inc.*, 934 F.3d 1344, 1351–54 (Fed. Cir. 2019). In *BTG*, combining prednisone and the CYP17 inhibitor abiraterone to treat prostate cancer was obvious because (i) prior art combined prednisone and the CYP17 inhibitor ketoconazole to manage prostate cancer; (ii) prednisone was already used to treat prostate cancer; and (iii) abiraterone was a more selective CYP17 inhibitor than ketoconazole and effectively suppressed testosterone. *BTG Int'l Ltd. v. Amneal Pharm. LLC*, 923 F.3d 1063, 1074–75 (Fed. Cir. 2019). Here, however, (i) no prior art combined valsartan and sacubitril; sacubitril with an ARB; or valsartan with a NEP inhibitor; (ii) sacubitril had never been administered to humans or studied

in hypertension or heart failure animal models; and (iii) no ARB, including valsartan, had been approved to treat heart failure. PFoF ¶¶ 48, 53, 73. Thus, valsartan and sacubitril were not both known to treat the same conditions. Plus, no ARB/NEP inhibitor combinations were in clinical development as of 2002, and the EP '072/Trippodo data suggested an ARB/NEP inhibitor was not desirable. PFoF ¶¶ 30–31, 35–36, 61, 75, 88. All told, comparing the facts here to *Nalpropion* and *BTG* only serves to highlight Defendants' hindsight and the nonobviousness of the claimed invention. *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1379 (Fed. Cir. 2012) ("[T]he proper analysis requires a form of amnesia that 'forgets' the invention and analyzes the prior art and understanding of the problem at the date of the invention."). Indeed, Defendants admitted their hindsight bias: they framed the relevant field broadly as treating hypertension or heart failure but used an ARB/NEP inhibitor combination as their starting point despite the numerous other options available. Tr. 531:2-19 (Closing). *See Insite Vision Inc. v. Sandoz, Inc.*, 783 F.3d 853, 859 (Fed. Cir. 2015) ("In considering motivation in the obviousness analysis, the problem examined is not the specific problem solved by the invention. Defining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness.") (cleaned up).

D. Defendants Selected Valsartan and Sacubitril with Hindsight

Even assuming a POSA had been motivated to combine an ARB and a NEP inhibitor, Trippodo/EP '072 disclosed neither valsartan nor sacubitril. Defendants take a piecemeal approach of relying on isolated disclosures of valsartan and sacubitril in other art. PFoF ¶¶ 48–49. Defendants misapprehend Novartis's dispute with this approach. *See* Op. Br. at 10–11. Novartis does not contend that a POSA must consider valsartan/sacubitril the most desirable combination. Nor does Novartis contend that a POSA must be motivated to select valsartan/sacubitril over some other ARB/NEP inhibitor combination. Instead, Novartis contends Defendants must (i) consider

the invention and the art as a whole, *In re Langer*, 465 F.2d 896, 899 (C.C.P.A. 1972), and (ii) provide some reason, suggestion, or motivation to combine valsartan and sacubitril in particular, *Forest Lab'ys, LLC v. Sigmapharm Lab'ys, LLC*, 918 F.3d 928, 934 (Fed. Cir. 2019).

Further, under their alternative obvious-to-try theory, Op. Br. at 9, 10, 13, Defendants cannot, as they have done here, make a beeline to valsartan and sacubitril. *Ortho-McNeil Pharm., Inc. v. Mylan Lab'ys, Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008) (finding that defendant failed to prove invention was obvious to try because defendant discounted the number and complexity of alternatives). Even if NEP inhibitors and ARBs were both known individually to treat hypertension or heart failure (which Defendants have not proven), Defendants have not alleged or cited any evidence that a POSA would have encountered a finite, small, or easily traversed number of options when identifying which ARB and NEP inhibitor to combine.

1. *The Data and Real-World Facts Show a POSA Would Not Have Identified Sacubitril or Sacubitrilat as a Desirable NEP Inhibitor to Combine with an ARB*

Defendants have not clearly and convincingly proven that a POSA would have identified sacubitril as a desirable NEP inhibitor. As of 2002, there were over 100 known NEP inhibitors, with about 50 having shown activity in preclinical models. PFoF ¶ 52. Dr. Fintel considered none of those. PFoF ¶ 57. He zeroed in on sacubitril, a NEP inhibitor that had never been administered to humans or tested in animal models of hypertension or heart failure. PFoF ¶ 53. The only two sacubitril references Dr. Fintel identified were the '996 patent and Ksander (published in 1995). PFoF ¶ 51; JTX 352 (Ksander); JTX 362 ('996 patent). In the decade after Novartis filed the '996 patent in 1992, NEP inhibitors had been abandoned as ineffective to treat hypertension and heart failure. PFoF ¶¶ 59–60. The '996 patent itself was abandoned in 1997. PFoF ¶ 60. And no one pursued further research with sacubitril. PFoF ¶ 60. These real-world facts would have

significantly curtailed the weight a POSA would have given to the '996 patent's statement that sacubitril was useful to treat hypertension or heart failure. PFoF ¶ 59; JTX 362 ('996 patent).

Defendants have repeatedly represented – incorrectly – that Ksander disclosed sacubitril as the "most active" or "most potent" NEP inhibitor in the prior art. Tr. 8:10–13 (Opening); Op. Br. at 1–2, 9, 10. Ksander did not compare sacubitril to other NEP inhibitors, which Dr. Fintel acknowledged. PFoF ¶ 54; Tr. 129:8-21 (Fintel). Nor could Dr. Fintel speculate how sacubitril stacked up to other NEP inhibitors (*i.e.*, to determine if there was a reason to prefer it) since he considered only Ksander and the '996 patent. PFoF ¶¶ 10, 51, 57. Although Ksander did compare the NEP inhibitor potency of sacubitril's active metabolite (sacubitrilat) to two known NEP inhibitors, sacubitrilat was not any more potent. PFoF ¶ 55. In other words, even if correct that sacubitrilat was the most potent NEP inhibitor Ksander synthesized, that did not set it apart from the more than 100 other NEP inhibitors disclosed in the prior art. PFoF ¶¶ 54, 55, 57. Nor did Dr. Fintel assert that potency for NEP inhibition would translate to biological activity, much less efficacy in treating hypertension or heart failure. PFoF ¶ 56. Thus, while Defendants need not prove a combination containing sacubitril was "the most desirable" (though that is the fact Defendants sought to prove),[2] they have failed to prove that sacubitril or sacubitrilat was a preferred NEP inhibitor alone or in combination with an ARB.

Last, it is not enough to allege sacubitril would have been obvious to try in place of SQ 28603 (the NEP inhibitor from Trippodo/EP '072). *Contra* Op. Br. at 9–10. Defendants do not assert any reason why a POSA would have wanted to replace SQ 28603 in the Trippodo/EP '072 combination; they merely point out that of the dozens of references cited, one reference in Ksander

[2] Just as Defendants need not prove sacubitril was the most desirable NEP inhibitor, it is not Novartis's burden to prove the nonobviousness by identifying a reason sacubitril was not desirable. *See Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 97 (2011); *contra* Op. Br. at 10.

(although not Trippodo or EP '072) studied SQ 28603. PFoF ¶ 58. It does not follow, as Defendants assert, that (i) a POSA would have been motivated to replace SQ 28603 or (ii) Ksander set out to or did identify NEP inhibitors superior to SQ 28603. *Contra* Op. Br. at 1–2, 9–10. Defendants argue that it would not be necessary to compare sacubitril to all known NEP inhibitors to identify sacubitril as interesting to try. *Id.* at 10. In support, Defendants cite Dr. Spinale's testimony (*id.*; Tr. 373:21–25 (Spinale)), but Dr. Spinale explained that whether a POSA would "need to perform a study with every single drug in a class in order to identify a preferred drug in that class" "depends upon the question being asked." Tr. 373:15–20 (Spinale). Defendants' counsel did not ask whether it would be necessary to test every single NEP inhibitor to identify sacubitril as interesting for further consideration. Even if it were not necessary to test every single NEP inhibitor, the evidence still would be insufficient to show sacubitril was obvious to try: Defendants do not assert that the NEP inhibitor class contained an easily traversed, finite, or small number of options—a predicate factual finding for Defendants' obvious-to-try theory. *In re Cyclobenzaprine*, 676 F.3d at 1072–73; *Sanofi-Aventis*, 748 F.3d at 1359–61.

Thus, Defendants failed to prove by clear and convincing evidence that a POSA would have selected sacubitril, either as a starting point or as a substitute for SQ 28603, in an ARB/NEP inhibitor combination to treat hypertension or heart failure.

2. *Defendants' Own References Fail to Support Their Assertion That a POSA Would Have Identified Valsartan as a Preferred ARB to Combine with a NEP Inhibitor*

Even assuming a POSA had been motivated to combine an ARB and a NEP inhibitor, a POSA would not have been motivated to select valsartan specifically. PFoF ¶ 62. First, Defendants do not assert, much less offer evidence, that the three properties they assert distinguish valsartan from other ARBs—potency, selectivity, and liver enzyme affinity—have clinical relevance, such

that they would have provided a motivation to combine valsartan with a NEP inhibitor. *See Tris Pharma, Inc. v. Actavis Lab'ys FL, Inc.*, No. 2021-1495, 2022 WL 2525318, at *3–*6 (Fed. Cir. 2022) (nonprecedential) (affirming nonobviousness where defendant failed to explain why a proposed modification would achieve the desired effect). For potency, Dr. Fintel cited Shetty—a study using tissue from rats without hypertension or heart failure that Dr. Fintel admitted showed no significant potency difference between valsartan and irbesartan. PFoF ¶¶ 65–66. Shetty disclosed that whether the potency differences would translate into a significant clinical advantage had not actually been determined. PFoF ¶ 66. For selectivity, Dr. Fintel cited Malacco—a study of valsartan and irbesartan. PFoF ¶ 67. But Malacco taught that selectivity did not appear to result in any differences between irbesartan and valsartan in the magnitude or duration of antihypertensive efficacy. PFoF ¶ 67. For liver enzyme affinity, Dr. Fintel cited Taavitsainen—an *in vitro* study on affinity for various CYP450 liver enzymes. PFoF ¶ 68; JTX 218 (Taavitsainen). Although Defendants broadly assert that valsartan's potential for drug-drug interactions was low, DFoF ¶ 37, neither Taavitsainen nor any other prior art taught that valsartan's potential for drug-drug interactions was low (just that valsartan's rate of interaction with drug-elimination enzymes was lower than two other ARBs). Nor did Taavitsainen provide any information on whether valsartan would interact adversely via other mechanisms or whether valsartan would safely interact with a NEP inhibitor. PFoF ¶ 68. Thus, Defendants have failed to show why potency, selectivity, or liver enzyme affinity would make valsartan a desirable ARB, or more importantly, why it was a desirable ARB to combine with sacubitril. *In re Langer*, 465 F.2d at 899 (obviousness analysis must consider the claimed invention as a whole).

Next, a POSA would not have been motivated to substitute valsartan for irbesartan in the Trippodo/EP '072 ARB/NEP inhibitor combination. PFoF ¶¶ 63, 69. To start, Defendants did not

provide any reason why a POSA would have wanted to modify the EP '072/Trippodo combination in the first place. PFoF ¶ 63. Nor did Defendants have a response to Dr. Spinale's explanation that a POSA would not have wanted to replace irbesartan with an ARB that was less effective in reducing blood pressure (e.g., valsartan). PFoF ¶ 69. As of 2002, valsartan was not preferred for treating hypertension or heart failure, and the literature contradicts Dr. Fintel's unsupported assertion that ARBs were poised to replace ACE inhibitors as the standard of care. PFoF ¶¶ 69, 74. The treatment guidelines available in 2002 identified ACE inhibition as the gold standard. PFoF ¶ 74. Dr. Spinale explained that his group followed the standard of care, which did not include the primary use of ARBs to treat heart failure. PFoF ¶ 74. That is consistent with Dr. Spinale's '217 patent, despite Defendants' misrepresentation otherwise, which identified valsartan as a preferred ARB "for use in the methods of the present invention"—"reducing pericardial fibrosis and adhesion formation," not treating hypertension or heart failure. PFoF ¶ 70; DTX 686 ('217 patent) at Abstract, col. 8, ll. 66–67. The Val-HeFT trial (Cohn) also reinforced the importance of ACE inhibition as the backbone and standard of care in heart failure. PFoF ¶ 71.

Thus, Defendants failed to prove by clear and convincing evidence that a POSA would have identified valsartan as a desirable ARB to combine with a NEP inhibitor.

E. A POSA Would Not Have Been Motivated to Combine EP '072, The '996 Patent/Ksander, and the '578 Patent/Diovan® Label to Achieve the Claimed Invention with a Reasonable Expectation of Success

Defendants offered two hindsight-driven theories in asserting the '659 patent claims are obvious over EP '072, the '996 patent/Ksander, and the '578 patent/Diovan® Label. Op. Br. at 12–13. The first starts with the EP '072 ARB/NEP inhibitor combination, replaces the NEP inhibitor with sacubitril from the '996 patent/Ksander, and replaces the ARB with valsartan from the '578 patent/Diovan® Label. *Id.* But EP '072 itself would have discouraged a POSA from combining an

ARB and a NEP inhibitor with a reasonable expectation of success, because the EP '072 data showed the combination failed to treat hypertension and would worsen heart failure. PFoF ¶¶ 19, 30–31, 35; *DePuy Spine*, 567 F.3d at 1326 ("An inference of nonobviousness is especially strong where the prior art's teachings undermine the very reason being proffered as to why a person of ordinary skill would have combined the known elements."). That negative data notwithstanding, Defendants use hindsight knowledge of the '659 patent claims to select valsartan and sacubitril without support, ignoring unfavorable data and discounting the number and complexity of the options. *Ortho-McNeil Pharm.*, 520 F.3d at 1364.

Defendants' "[a]lternative" theory starts with sacubitril from the '996 patent/Ksander and valsartan from the '578 patent/Diovan® Label and combines them based on EP '072, Op. Br. at 13, but this is even worse from a legal perspective because it starts with the '659 patent claim elements and works backwards. *See Mintz*, 679 F.3d at 1379 (obviousness analysis requires fact-finder to "forget" the invention); *Merck Sharp & Dohme B.V. v. Warner Chilcott Co.*, 711 Fed. App'x 633, 637 (Fed. Cir. 2017) (using the patent-in-suit "as a roadmap . . . represents an improper reliance on hindsight"). Also, framing this pathway as consistent with a standard practice of combining drugs with different mechanisms of action, Op. Br. at 13, does not solve the hindsight problem, because Dr. Fintel admitted that such combinations could be detrimental, and to find out a POSA would have to test the combination at a time when no one was pursuing clinical development of ARB/NEP inhibitor combinations. *Supra* § II.C. Thus, the valsartan/sacubitril combination is not made obvious by a motivation to find and test a new ARB/NEP inhibitor combination. *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 997 (Fed. Cir. 2009) ("[P]atents are not barred just because it was obvious to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only

general guidance as to the particular form of the claimed invention or how to achieve it.") (internal citation omitted).

Finally, there is no dispute that reasonable expectation of success is tied to the scope of the '659 patent claims – pharmaceutical compositions combining valsartan and sacubitril in about a 1:1 weight ratio. *See Teva Pharm. USA, Inc. v. Corcept Therapeutics, Inc.*, 18 F.4th 1377, 1381 (Fed. Cir. 2021). But there are two reasons why Defendants' evidentiary burden still depends on showing a reasonable expectation of successfully treating hypertension or heart failure by clear and convincing evidence. First, claim 2 requires the pharmaceutical composition to contain valsartan and sacubitril in "amounts effective to treat hypertension or heart failure," and thus for this claim, a POSA must have a reasonable expectation of success in achieving that end. *Id.* Second, and for all asserted claims, the motivation to combine that Defendants assert is a motivation to treat hypertension or heart failure. *See e.g.*, Op. Br. at 10; PFoF ¶ 8. And if a POSA had no reasonable expectation that combining valsartan and sacubitril would treat hypertension or heart failure, a POSA would not have been motivated to combine them in the first place. PFoF ¶ 22. *See Intelligent Bio-Systems, Inc.*, 821 F.3d at 1368 (finding that a lack of reasonable expectation of quantitative deblocking "is irrelevant to a finding that there was no reasonable expectation of success in meeting the claims . . . , which do not require quantitative deblocking at all, it is central to a finding of no motivation to combine. This is because the petitioner's *sole* argument for why one of skill in the art would be motivated to combine" two references was to achieve "quantitative deblocking"); *DePuy Spine*, 567 F.3d at 1326.

In sum, Defendants have failed to prove by clear and convincing evidence that a POSA would have been motivated to combine EP '072, the '996 patent/Ksander, and the '578 patent/Diovan® Label to achieve the claimed invention with a reasonable expectation of success.

F. Objective Evidence of Nonobviousness Shows Defendants' Hindsight

Each piece of Novartis's objective evidence, and all the more persuasive when combined, confirms the nonobviousness of the '659 patent claims and that Defendants used hindsight to reconstruct the claimed valsartan/sacubitril combination. "[E]vidence of secondary considerations may often be the most probative and cogent evidence in the record," and "guard[s] against slipping into use of hindsight." *Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1052–53 (Fed. Cir. 2016) (en banc) (cleaned up).

1. *Others Failed to Develop or Abandoned ARB/NEP Inhibitor Combinations*

As of 2002, there had been many attempts to improve outcomes in heart failure patients and many heart failure drugs were in clinical development. PFoF ¶ 85. But most drugs had failed, and developing successful new heart failure drugs was called an "[i]mpossible [t]ask." PFoF ¶ 86. In particular, by 2000, BMS had abandoned its EP '072 patent application disclosing an ARB/NEP inhibitor combination, and as of 2002, no ARB/NEP inhibitor combination had progressed to clinical development. PFoF ¶¶ 87–88. Defendants provided no evidence for their main rebuttal to these failures and abandonment—that the valsartan patent (the '578 patent) could or would have deterred others from pursuing combinations containing valsartan. Op. Br. at 15. This Court recognized as much, and the parties agreed before trial they would not present testimony from economics experts. Tr. 531:20–532:9 (Closing); C.A. 20-md-02930-RGA, D.I. 760. Regardless, no one pursued an ARB/NEP inhibitor combination after the Trippodo/EP '072 disclosure. PFoF ¶¶ 35, 44–45, 87–88. Also, Novartis abandoned its '996 sacubitril patent in 1997, and there is no evidence that anyone else pursued any combination containing sacubitril. PFoF ¶ 89.

This objective evidence of failure and abandonment undermines Defendants' assertion that combining valsartan and sacubitril would have been an obvious solution to treat heart failure.

Symbol Techs., Inc. v. Opticon, Inc., 935 F.2d 1569, 1578–79 (Fed. Cir. 1991) ("the failure of others to find a solution to the problem which the patent[s] in question purport[] to solve" "shows indirectly the presence of a significant defect [in the prior art], while serving as a simulated laboratory test of the obviousness of the solution to a skilled artisan.") (internal citation omitted).

2. *The Claimed Invention's Results in Heart Failure and Hypertension Would Have Been Unexpected as of 2002*

As of 2002, a POSA would have been surprised that the claimed combination would have such profound effects in hypertension and treating heart failure. PFoF ¶ 92. Entresto®'s results in treating HFrEF in adults, HFrEF in children, and HFpEF would have been unexpected because (i) sacubitril had never been administered to humans or studied in heart failure animal models; (ii) no ARB, including valsartan, had been approved to treat heart failure or used at all to treat HFpEF or children; (iii) no ARB/NEP inhibitor combinations were in clinical development as of 2002; and (iv) the only data for an ARB/NEP inhibitor combination in a model of heart failure showed the combination worsened heart function. PFoF ¶¶ 53, 93–96, 116–118, 121–123. The antihypertensive effect of a valsartan/sacubitril combination in a hypertensive animal model would have been unexpected given the EP '072 ARB/NEP inhibitor hypertension model failure; and it was undisputed that the valsartan/sacubitril combination was synergistic (*i.e.*, the combination's antihypertensive effect was greater than the sum of its parts). PFoF ¶¶ 133–135. Novartis's evidence supporting unexpected results is set forth in full in ¶¶ 91–139 of its Findings of Fact, and Defendants do not dispute there is a nexus between these results and the '659 patent claims.

Rather, Defendants first rehash their prima facie obviousness argument based on *Nalpropion*, but the facts here do not fit with *Nalpropion* because the '659 patent inventors did not combine two drugs known to treat hypertension or heart failure. *Supra* § II.C; *contra* Op. Br. at 14. Even if valsartan and sacubitril were both known individually to treat hypertension or heart

failure (which Defendants have not proven), this Court must still determine whether a POSA would have been surprised at the type and magnitude of the claimed combination's effects. *Sanofi-Aventis*, 748 F.3d at 1360-61. Novartis's unexpected results are based on an undisputedly novel drug combination—no prior art disclosed combinations of valsartan and sacubitril, sacubitril with an ARB, or valsartan with a NEP inhibitor. PFoF ¶ 48. Defendants' remaining objective indicia arguments raise piecemeal disputes with evidence, but those disputes are either factually wrong, legally deficient, or both.

First, Defendants fault Novartis for failing to compare the invention's results to the closest prior art, which Defendants did not identify until after the close of evidence. Op. Br. at 14. Defendants identified "either valsartan or sacubitril and valsartan" as the closest prior art. Tr. at 563:12–14 (Closing). But it is not possible for Novartis to compare the invention's results to the invention itself (valsartan and sacubitril in about a 1:1 weight ratio) or any other valsartan/sacubitril combination that indisputably did not exist prior to 2002. PFoF ¶ 48. *See Millennium Pharm., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1368 (Fed. Cir. 2017) (finding that patentee was not required to compare results to a product that "was not specifically disclosed, prepared, or tested in the" prior art). That leaves valsartan, which as of 2002, was not approved to treat any kind of heart failure. PFoF ¶ 73. And no ARB had been shown to be superior to ACE inhibition—the standard of care for heart failure as of 2002. PFoF ¶¶ 71, 74, 94. In any event, Dr. Spinale compared the invention's results to Dr. Fintel's three categories of prior art, including valsartan. PFoF ¶ 92. *See Tris Pharma, Inc. v. Actavis Lab'ys FL, Inc.*, 755 Fed. App'x 983, 992 (Fed. Cir. 2019) (finding district court erred in rejecting patentee's evidence of unexpected results where the patentee compared invention's results to products cited by patent challenger and where no party asserted one of those products represented the closest prior art).

Second, Defendants attacked various results as not unexpected based on what a POSA would know today, rather than as of 2002. For example, Defendants conclude that Entresto®'s results are not unexpected compared to the valsartan results in Solomon 2019 (PARAGON-HF clinical trial for HFpEF) or Mann 2022 (LIFE clinical trial for end-stage HFrEF). Op. Br. at 14. And Defendants argue that Entresto®'s results in children with HFrEF are not unexpected based on the 2014 results in adults with HFrEF disclosed in McMurray. DFoF ¶ 66. All three arguments incorrectly compare Entresto®'s results to what is known *today*, not what was known in 2002. PFoF ¶¶ 103, 113, 120, 150. *Forest Lab'ys*, 918 F.3d at 937 ("While we have permitted evidence from after the patent is granted to be considered in assessing . . . unexpected results, the results must be unexpected by [a POSA] *at the time of the application*.") (cleaned up, emphasis added).

Third, Defendants' criticism of the unexpected antihypertensive effect reported by Dr. Webb is indefensible given that the experts agreed that the EP '072 ARB/NEP inhibitor combination failed to lower blood pressure in an animal model of hypertension. *Supra* § II.A.1. The valsartan/sacubitril combinations that inventor Randy Webb tested in an animal model of hypertension not only had an antihypertensive effect, that effect also was synergistic. PFoF ¶ 135. In other words, a valsartan/sacubitril combination in a 1:1 weight ratio had a greater antihypertensive effect than the sum of the effects of sacubitril alone and valsartan alone. PFoF ¶¶ 135–136. That directly contradicts Defendants' assertion that Novartis did not present any evidence that the claimed 1:1 weight ratio achieved unexpected results, *see* Op. Br. at 13, and is contrary to the requirement that objective evidence relate to the claimed invention as a whole, not to specific claim elements. *See WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1330-32 (Fed. Cir. 2016) ("Requiring patentees to prove that objective evidence is tied to a specific claim element—and only that claim element—runs counter to the statutory instruction that the obviousness analysis

involves determining whether '*the claimed invention as a whole* would have been obvious.'") (citing 35 U.S.C. § 103).

Fourth, Defendants criticize the HFrEF evidence (based on McMurray) as an indirect comparison to ACE inhibition, which was not the closest prior art. Op. Br. at 14. But Defendants' criticism is neither logical nor legally sound. The PARADIGM-HF clinical trial demonstrated that Entresto® is substantially better in reducing the risk of morbidity and mortality than the ACE inhibitor enalapril, the gold standard in treating HFrEF as of 2002. PFoF ¶¶ 97–102. Since Entresto® is substantially better than the gold standard as of 2002, then it is substantially better than valsartan, which was *not* the gold standard as of 2002. PFoF ¶ 114. Thus, comparing Entresto® to the 2002 gold-standard is an indirect, but legally permissible, way to prove unexpected results. *See In re Merchant*, 575 F.2d 865, 869 n.8 (C.C.P.A. 1978) (indirect comparisons to the closest prior art can be persuasive evidence of unexpected results); *In re Depomed Patent Litig.*, No. 13-4507, 2016 U.S. Dist. LEXIS 166077, at *242–43 (D.N.J. Sept. 30, 2016) (comparing the claimed invention to the "gold standard" is "legally probative" of unexpected results).

Finally, Defendants try to poke holes in the HFrEF and HFpEF clinical trials, seemingly to show the unexpected results apply only to "select subgroups" of patients and thus are not commensurate in scope with the asserted claims. Op. Br. at 14. For example, Defendants insinuate that the FDA rejected Novartis's application for an indication directed to HFpEF. Op. Br. at 14. Not so. After the Entresto® clinical trial in HFpEF patients and the follow-up LVEF analysis in Solomon 2020 (which Dr. Fintel did not even address), the FDA expanded the Entresto® label to cover HFpEF, which Dr. Fintel agreed the FDA would do only if it determined Entresto® was effective for that indication. PFoF ¶¶ 124–126; Tr. 499:11–19 (Fintel). Defendants also state that the LIFE clinical trial showed Entresto® was not superior to valsartan in heart failure, Op. Br. at

14, but Defendants leave out that the LIFE clinical trial enrolled only a subset of the most severe HFrEF patients, ended early due to COVID-19, and was not designed (was statistically underpowered) to determine if Entresto® is superior to valsartan in reducing HFrEF morbidity and mortality, PFoF ¶ 104. Thus, Defendants' scope arguments fail on the facts, because unexpected results are not commensurate only if "the evidence [is] plainly disproportionate to the scope of the claim." *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1308–09 (Fed. Cir. 2011). And Defendants ignore that the claims are pharmaceutical composition claims, and for such claims, showing unexpected superiority for one property is sufficient. *See In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987).

3. *Entresto® Met a Long-Felt Need for New Heart Failure Treatments*

Entresto® met long-felt needs for new treatments for HFpEF in adults and HFrEF in adults and children. PFoF ¶¶ 140–144, 146–152. Defendants disagree, asserting that (i) there was no long-felt need as of 2002 because valsartan had already met it, or (ii) assuming there was a long-felt need as of 2002, the need still remains because some patients taking Entresto® still get hospitalized and die. Op. Br. at 14; DFoF ¶ 75.

First, as of 2002, valsartan had not met a long-felt need for new treatments for HFpEF in adults and HFrEF in adults and children, because valsartan was (i) not approved for heart failure of any type; (ii) not a first-line therapy for heart failure of any type; and (iii) not shown to be any better than the standard of care as of 2002. PFoF ¶ 145. It had not even been tested or used in children or HFpEF. PFoF ¶¶ 118, 123; *see Sanofi v. Glenmark Pharm. Inc.*, 204 F. Supp. 3d 665, 695 (D. Del. 2016) (Andrews, J.) (finding there was a long-felt need for the claimed method of treatment, even with other drugs of the same class on the market because "[i]t ha[d] been notoriously difficult to develop a drug with high efficacy . . . with a favorable side effect profile").

Second, Entresto® met the long-felt needs for new treatments, and a drug can meet a long-felt need, even if it is not a cure. *See Pfizer Inc. v. Watson Pharm., Inc.*, 920 F. Supp. 2d 552, 562 (D. Del. 2013) (Andrews, J.) ("Here, Pfizer has shown that [prior art compounds] are nephrotoxic while rapamycin is not, such that rapamycin meets a need that its predecessors have not. Rapamycin met a long felt need, even if on a small scale."). Dr. Fintel admitted Entresto® is "a very good drug" and that he prescribes it for HFrEF because it is superior to the previous standard of care. PFoF ¶ 156; Tr. 501:12–24 (Fintel). Consistent with this, industry leaders—including the FDA—concluded Entresto® satisfied long-felt needs for new treatments for HFpEF in adults and HFrEF in adults and children. PFoF ¶¶ 142–143, 148, 152.

4. *Industry Leaders Praised Entresto®*

"Well-known and well-respected" cardiologists, including Dr. Fintel's superior at Northwestern University, praised Entresto®'s efficacy for treating heart failure. Tr. 496:6–12 (Fintel); PFoF ¶¶ 154–155; *Apple Inc.*, 839 F.3d at 1053 (explaining that industry praise of a "claimed invention or a product that embodies the patent claims weighs against an assertion that the same claimed invention would have been obvious"). None of the praise Novartis offered at trial was by a Novartis employee, despite Defendants' suggestion otherwise. Op. Br. at 14; *see also Arctic Cat Inc. v. Bombardier Recreational Prods. Inc.*, 876 F.3d 1350, 1364–65 (Fed. Cir. 2017) (jury's presumed finding of industry praise was supported by substantial evidence even where praise from third party was published in patentee's press release). Defendants also deride the Prix Galien prize, asserting it is not probative of nonobviousness because it is not a Nobel Prize and Novartis (like every other company) paid to be on the nomination list. Op. Br. at 14; DFoF ¶ 76. None of that detracts from the fact that industry, academic, and non-profit leaders selected Entresto® as the winner of the best pharmaceutical agent in 2021. PFoF ¶ 157.

III. DEFENDANTS HAVE FAILED TO PROVE NON-ENABLEMENT

The sole enablement issue is whether the '659 patent was required to enable a combination of valsartan and sacubitril in the form of a complex, which undisputedly would not have been known or contemplated by a POSA as of the 2002 priority date. The answer is no. Under *Hogan*, enablement must be judged as of a patent's priority date, and a later-existing state of the art cannot be used to reach back and invalidate a patent for lack of enablement. Applying this doctrine, the '659 patent is properly enabled. Defendants present no clear and convincing evidence otherwise. Defendants' brief sets forth two theories for why the '659 patent is not enabled, but both fail.

First, Defendants argue that the portion of *Hogan* relied on by Novartis is not controlling precedent. To the contrary, *Hogan*'s key holding relevant here is binding authority that this Court should follow, not *dicta*. *Contra* Op. Br. at 2, 20–23, 25. Moreover, *Chiron* and *U.S. Steel* are additional binding Federal Circuit authority holding that a later-existing state of the art cannot be used to invalidate a patent for lack of enablement. Defendants have not even argued otherwise. *See* Op. Br. at 26 n. 3 (acknowledging *Chiron*'s holding).

Second, Defendants argue that the *Hogan* enablement doctrine does not apply on the facts of this case. Defendants are wrong. No other case is closer to the facts here than *Hogan*. And none of Defendants' evidence suggests that a POSA in 2002 with the '659 patent in hand would have foreseen that a complex of valsartan and sacubitril was something that could be explored or would even be possible to make, because the relevant technology was unknown (not nascent). In fact, Defendants admit "a POSA reviewing the specification as [of] the priority date would not have contemplated, foreseen, or envisioned such complexes." Op. Br. at 29. The facts in this case are analogous to those of *Hogan*, the earliest application in *Chiron*, and *U.S. Steel*, and like in those cases, the claims here are enabled.

Novartis's later, nonobvious discovery of valsartan and sacubitril in the form of a complex should not invalidate the '659 patent claims to Novartis's earlier invention: the novel combination of valsartan and sacubitril. Considering a later state of the art with respect to enablement, which Defendants ask the Court to do here, would effectively preclude inventors from obtaining patents on base inventions. Such a holding would frustrate the well-settled practice of obtaining appropriate patents on base inventions and subsequent appropriate patents on improvement and selection inventions, which build on that innovative base. Moreover, allowing a later-discovered embodiment to reach back in time and invalidate a previously valid patent would cause substantial uncertainty. The '659 patent was enabled as of its 2002 priority date, and under the law, it remains enabled even after publication of Novartis's further work on valsartan and sacubitril combinations.

Defendants have not met their burden of showing that the claims of the '659 patent lack enablement by clear and convincing evidence.

A. The *Hogan* Doctrine Is Controlling Precedent, Not Dicta

1. *Under Hogan and Its Progeny, a Later-Existing State of the Art May Not Be Used to Invalidate a Patent for Lack of Enablement*

As Judge Markey of the Court of Customs and Patent Appeals ("CCPA") (the Federal Circuit's predecessor court) first articulated in *Hogan*, and the Federal Circuit followed in both *Chiron* and *U.S. Steel*, lack of enablement may not be asserted based on "knowledge about later art-related facts . . . which did not exist on the filing date." *In re Hogan*, 559 F.2d 595, 604–06 (C.C.P.A. 1977); *Chiron Corp. v. Genentech, Inc.*, 363 F.3d 1247, 1254 (Fed. Cir. 2004) ("The law does not expect an applicant to disclose knowledge invented or developed after the filing date."); *U.S. Steel Corp. v. Phillips Petroleum Co.*, 865 F.2d 1247, 1251–52 (Fed. Cir. 1989) (holding evidence that "was directed solely to a later state of the art" was "immaterial to the section 112, first paragraph inquiry" and an application's "sufficiency under § 112, first paragraph, must

be judged as of the filing date"). The following facts of *Hogan*, *Chiron*, and *U.S. Steel* illustrate this doctrine.

In *Hogan*, the applicants claimed a "solid polymer." The specification enabled preparation of a crystalline form of that polymer, which was the sole form of the polymer known as of the patent's filing date. *Hogan*, 559 F.2d at 604–06. The USPTO rejected the claims as non-enabled because they also covered a non-crystalline (amorphous) form of the polymer, yet the patent failed to enable that non-crystalline form, which was first made years after the patent application was filed. *Id.* at 605. The CCPA reversed and remanded the case back to the USPTO, explaining that the specification should have been tested for compliance with the enablement requirement as of the priority date, and that a later-existing state of the art cannot be used to invalidate a patent for lack of enablement. *Id.* at 604–07; Op. Br. at 21. Said another way, if a patent was enabled as of its priority date, considering "all art-related facts existing [as of the priority date], then the fact of that enablement was established for all time and a later change in the state of the art cannot change it." *Id.* at 605. *Hogan* held that the USPTO had erred by basing the enablement rejection on a later-existing state of the art. *Id.* at 604–05.

In *Chiron*, the claims were broadly directed, in functional rather than structural terms, to all monoclonal antibodies that bound to a specified antigen and had been construed to embrace both murine and chimeric antibodies. *Chiron*, 363 F.3d at 1250–52. The earliest patent application at issue (the 1984 application) disclosed murine antibodies but not chimeric antibodies. *Id.* at 1251, 1254. The Federal Circuit held that "[b]ecause the first publication documenting the successful creation of chimeric antibodies occurred after the filing of the [earliest] application, . . . this new technology arose after the [1984] filing date and thus was, by definition, outside the bounds of the enablement requirement." *Id.* at 1254 (citing *Hogan*, 559 F.2d at 605–06).

In *U.S. Steel*, the claims were to a polypropylene that had been construed by the district court not to be limited to any particular intrinsic viscosity or molecular weight. *U.S. Steel*, 865 F.2d at 1249–50; *Phillips Petroleum Co. v. U.S. Steel Corp.*, 673 F. Supp. 1278, 1346 (D. Del. 1987). The Federal Circuit determined that the defendants' evidence of a later-discovered polypropylene having a higher viscosity and higher molecular weight than was disclosed in the specification was "immaterial" to enablement, because "[t]he record evidence[d] that until [after the relevant date], no one thought it possible that propylene monomers could be polymerized into polypropylene with [those characteristics]." *U.S. Steel*, 865 F.2d at 1249–52.

Hogan, *Chiron*, and *U.S. Steel* all stand for the same proposition that enablement is judged as of the priority date, and a later-existing state of the art (*i.e.*, knowledge about later art-related facts) may not be properly considered in the enablement analysis.

2. *Defendants' Arguments Fail That Hogan's Enablement Doctrine Is Not Binding Authority*

Defendants propose various reasons why *Hogan*'s enablement statements discussed above were dicta, but none is supported by the case law. In fact, Defendants themselves recognize that their position goes against the Federal Circuit's *Chiron* decision. Op. Br. at 26 n. 3 (explaining that the *Chiron* majority did not treat *Hogan*'s analysis as dicta). And despite their dicta arguments, Defendants repeatedly acknowledge a Federal Circuit exception to the "full scope" enablement requirement for enabling technology and concepts that are "unknown" to the POSA as of the priority date. *See* Op. Br. at 22, 24–26.

Defendants' first argument, that *Hogan* did not decide infringement, is inapposite (*contra* Op. Br. 21–22). *Hogan* held that the USPTO had erred in considering the later-existing state of the art in its enablement analysis, even if the claims covered the later embodiment (*i.e.*, even assuming there was infringement). *See Hogan*, 559 F.2d at 604–05; Op. Br. at 21 (acknowledging that "[t]he

CCPA [in *Hogan*] reversed on the basis that enablement is determined as of the effective filing date, and that a later existing state of the art cannot demonstrate a lack of enablement"). Moreover, *Hogan* implicitly found that the claims covered the later embodiment, because otherwise, enablement would not have been an issue to decide (subject matter outside claim scope need not be enabled). In any event, both *Chiron* and *U.S. Steel* addressed claims construed to encompass the later embodiments, and those cases stand for the same proposition as *Hogan*—that a later-existing state of the art may not be properly considered in the enablement analysis. *Supra* § III.A.1.

Second, neither the *Hogan* majority nor concurring opinion suggests that the portion of *Hogan* relied on by Novartis was dicta. *Contra* Op. Br. at 20–23. The point that the *Hogan* majority expressly "[did] not reach" was whether the "pioneer" status of an invention is relevant to the enablement inquiry, which is separate from *Hogan*'s holding that enablement must be evaluated as of the priority date and that a later state of the art cannot be used to challenge enablement. *See Hogan*, 559 F.2d at 606, *see also* 601 n. 10. The portion of the majority opinion that the *Hogan* concurring opinion referred to as "extended dicta" was likewise related to policy reasons for granting protection to "pioneer" inventions. *See Hogan*, 559 F.2d at 610 (Miller, J., concurring in part). Novartis is not relying on the "pioneer" invention portion of the *Hogan* opinion, and the Court need not do so either to find in favor of Novartis. Moreover, the *Hogan* concurrence agreed with the majority, finding it "properly h[eld] that the board erred in considering the *later state of the art* in testing for compliance with the enablement requirement." *See id.* at 609 (Miller, J., concurring in part) (emphasis in original).

Third, Defendants wrongly assert that *Hogan* was "remanded for other reasons" than the statements Novartis relies on, and therefore the statements Novartis cites are dicta. Op. Br. at 23 citing *Hogan*, 559 F.2d at 604–05. Defendants cite the following statement from *Hogan*:

> Because the board did not consider appellants' ancestral applications [to which the application at issue claimed priority] in affirming the rejections under § 112, first paragraph, in view of the cited references, those rejections must be reversed, and the case remanded to permit consideration of enablement questions as of the proper filing date.

Hogan, 559 F.2d at 604–05. Contrary to Defendants' argument, the reason that the correct filing date mattered was that the USPTO improperly cited in its enablement analysis evidence of later art-related facts that did not exist as of the earlier filing date. *See Hogan*, 559 F.2d at 604–05. The CCPA thus remanded to the USPTO to reconsider enablement as of the priority date, and without resort to the later state of the art, which is the same *Hogan* enablement doctrine that Novartis cites.

Finally, that *Hogan* was decided 45 years ago is inapposite (*contra* Op. Br. at 20), because *Hogan* has never been overturned. *See Deckers Corp. v. U.S.*, 752 F.3d 949, 964 (Fed. Cir. 2014) ("[W]e as a panel are bound by prior CCPA decisions unless and until those CCPA decisions are overturned en banc or through Supreme Court intervention. . . ."). *Hogan*, like all CCPA cases, was decided en banc. *See id.* at 962 ("[T]he five-judge CCPA . . . always sat en banc as a five-judge panel."). *Hogan*, which bound the Federal Circuit in *Chiron*, "is binding unless overruled en banc." *Chiron*, 363 F.3d at 1257.

Defendants' dicta argument is also undermined by both *Chiron* and *U.S. Steel*, which cited *Hogan* as binding precedent. *See Chiron*, 363 F.3d at 1254 (explaining "[t]he law does not expect an applicant to disclose knowledge invented or developed after the filing date" citing *Hogan*, 559 F.2d at 605–06); *U.S. Steel*, 865 F.2d at 1251–52 (finding the defendants' "misdirected approach," based on evidence "directed solely to a later state of the art," was "the same as that improperly relied on by the PTO in *Hogan*"). Defendants' argument is also not supported by *Plant Genetic* (*contra* Op. Br. at 24–25), which identifies as dicta only the statements in *Hogan* regarding "pioneer" inventions being entitled to "broad scope," and not *Hogan*'s core holding, which

Novartis relies upon, that enablement must be evaluated as of the priority date and cannot be attacked based upon a later state of the art. *Plant Genetic Sys. v. Dekalb Genetics Corp.*, 315 F.3d 1335, 1340–41, 1344 (Fed. Cir. 2003).

Consistent with the fact that *Hogan* is binding authority, other district courts (even as recently as three months ago) have applied *Hogan*'s holding that a later-existing state of the art may not be used to invalidate a patent for lack of enablement. *Merck Sharp & Dohme LLC v. Mylan Pharm. Inc.*, No. 1:19CV101, 2022 U.S. Dist. LEXIS 195204, *107, 109–113 (N.D. W. Va. Sept. 21, 2022) (citing *Hogan* in finding a claim to a salt "or a hydrate thereof" not invalid for lack of enablement where the specification disclosed the only then-known hydrate but the experts acknowledged the "possibility" of discovering additional hydrates)[3]; *Regents of the Univ. of Cal. v. Dako N. Am., Inc.*, No. C 05-03955 MHP, 2009 WL 1083446, *16–*18 (N.D. Cal. April 22, 2009) (citing *Hogan* in denying summary judgment of non-enablement where the patent did not teach a later-invented diagnostic measure that "was not achieved, or indeed even possible, . . . at the time the . . . application was filed").

3. *Defendants' "Full Scope" Enablement Cases Are Consistent with Hogan*

Defendants' "full scope" enablement cases (*AK Steel*, *ALZA*, *Chiron*, *Fisher*, *Liebel-Flarsheim*, *MagSil*, *Plant Genetic*, and *Trustees of Boston*) are easily reconcilable with the *Hogan* doctrine. Each found the claim(s) at issue lacked enablement based on the state of the art that existed as of the relevant filing date, not a later state of the art as prohibited by *Hogan*.

In *Plant Genetic* and for the later applications in *Chiron*,[4] the prior art expressly

[3] The claims in *Merck* had been construed by this Court during related multidistrict litigation. *Merck*, 2022 U.S. Dist. LEXIS 195204, *15–16.

[4] In *Chiron*, the Federal Circuit reached different enablement conclusions concerning the earliest 1984 application, which was enabled as discussed above (*supra* § III.A.1) and the later 1985 and

contemplated the non-enabled embodiments. *Plant Genetic*, 315 F.3d at 1340 (stably transformed monocot plant cell not enabled where the patentee asserted monocot cells were "already being stably transformed" in the prior art and "were highly desirable"); *Chiron*, 363 F.3d at 1251 (chimeric antibodies not enabled by later applications because chimeric antibody technology was "known in [that] art field" by the time of those applications), 1256 (patentee argued that by the last application date "chimeric antibodies were so well known that they had become routine technology" and thus did not need to be specifically enabled).

In *AK Steel* and *Liebel-Flarsheim*, the patents themselves contemplated the non-enabled embodiments by teaching away from them. *AK Steel Corp. v. Sollac & Ugine*, 344 F.3d 1234, 1236–38, 1244 (Fed. Cir. 2003) (aluminum coating having 8.0%–8.5% silicon not enabled because the specification "clearly and strongly warn[ed]" that a coating having more than 0.5% silicon would not work); *Liebel-Flarsheim Co. v. Medrad, Inc.*, 481 F.3d 1371, 1379 (Fed. Cir. 2007) (method using syringe without a pressure jacket not enabled because the specification "[taught] away" from such syringes by stating they were "impractical").

In *ALZA*, *MagSil,* and *Trustees of Boston*, the patentees asserted that the non-enabled embodiments were in fact enabled by the patent specifications in view of the prior art. *ALZA Corp. v. Andrx Pharm., LLC*, 603 F.3d 935, 937, 939 (Fed. Cir. 2010) (non-osmotic dosage forms not enabled even though the patentee "assert[ed] that creating non-osmotic dosage forms . . . was well known to a [POSA]" and "the specification provide[d] sufficient guidance regarding [such] forms"); *MagSil Corp. v. Hitachi Global Storage Techs., Inc.*, 687 F.3d 1377, 1382 (Fed. Cir. 2012) (device forming a junction with a resistance change greater than 10% not enabled even

1986 applications, which were not enabled, due to intervening changes in the relevant state of the art. *See Chiron*, 363 F.3d at 1254–57.

though the patentee argued a POSA could work from the specification to make junctions with a resistive change between 100% and 120% without undue experimentation); *Trustees of Boston Univ. v. Everlight Elecs. Co.*, 896 F.3d 1357, 1362–63 (Fed. Cir. 2020) (a semiconductor having a monocrystalline growth layer formed directly on an amorphous buffer layer not enabled where the patentee argued this embodiment could be realized following the teachings of the specification).

Finally, *Hogan* is also consistent with the CCPA's earlier decision in *Fisher*, which set forth general enablement principles but did not address enablement in view of a later state of the art. *In re Fisher*, 427 F.2d 833, 836, 839 (C.C.P.A. 1970); *Hogan*, 559 F.2d at 606. None of Defendants' cited cases changes the applicability of *Hogan* here or undercuts the enablement of the '659 patent claims as of the time the patent was filed.[5]

B. The Claims Are Enabled in View of the State of the Art as of the '659 Patent's Priority Date

1. *The POSA Would Not Have Had Solid-State Chemistry Experience or Knowledge of Complexes*

Enablement must be judged from the perspective of a POSA in view of the pertinent art as of 2002. *See W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1556 (Fed. Cir. 1983); *see also Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 448–49 (Fed. Cir. 1986) (The POSA is a "hypothetical person who is presumed to be aware of all the pertinent art.").

A preliminary issue is what POSA definition should be applied in the enablement analysis. The parties' POSA definitions differ in one key aspect that is relevant to the knowledge that a POSA would have had as of the 2002 priority date and the art that was pertinent to the POSA.

[5] Novartis reserves the right to address an opinion in *Amgen Inc. v. Sanofi*, No. 21-757 (U.S.), currently pending before the Supreme Court, if relevant to the enablement issues in this case.

Infra §§ III.B.3–4. Defendants argue that a POSA would have had experience and knowledge in solid-state chemistry (*i.e.*, the area of chemistry involved in making complexes), while Novartis proposes that a POSA would not have had experience, familiarity, or interest in solid-state chemistry. PFoF ¶¶ 164–165; DFoF ¶ 9. While the definition of the POSA impacts the enablement analysis, the Court should hold that Defendants failed to prove non-enablement by clear and convincing evidence regardless of which definition the Court adopts. *Infra* §§ III.B.3–4.

As the '659 patent demonstrates, and as confirmed by Defendants' medical expert Dr. Fintel, the POSA would not have had experience, familiarity, or interest in solid-state chemistry—in line with Novartis's POSA definition—and such art would not be part of the "pertinent art" of which a POSA is aware. Dr. Fintel agreed that the field of art for the '659 patent is the treatment of hypertension and heart failure. PFoF ¶ 166. The specification generally relates to pharmaceutical compositions and methods of using those compositions for treating hypertension or heart failure. PFoF ¶ 168. Consistent with this, the '659 patent explains that the combination of valsartan and sacubitril was developed to address a need for an improved therapy for the treatment of heart failure or hypertension, not a solid-state chemistry problem. PFoF ¶ 169; *see Best Medical Int'l, Inc. v. Elekta Inc.*, 46 F.4th 1346, 1353 (Fed. Cir. 2022) (explaining relevant factors for determining the level of skill in the art include the "type of problems encountered in the art" and "[t]he patent's purpose"); *Bausch*, 796 F.2d at 449 (pertinent art is that "reasonably pertinent to the particular problem with which the inventor was involved").

The '659 patent claims a pharmaceutical composition containing a novel combination of valsartan and sacubitril. PFoF ¶ 170. The claims do not include any element directed to non-covalently linking valsartan and sacubitril, and the specification does not disclose or even suggest complexes. PFoF ¶¶ 171, 174, 180, 183. During claim construction, Judge Stark declined to limit

the claims of the '659 patent to valsartan and sacubitril as two separate components, which would have excluded valsartan and sacubitril in the form of a complex. JTX 14 (Markman Opinion) at 5–7. But this construction does not suggest that the form of the claimed combination is somehow material to the claimed invention or an element of the claims; it is not. PFoF ¶¶ 173–174.

Defendants rely on hindsight to improperly redefine the POSA as having knowledge beyond the pertinent art. Defendants' only evidence for including solid-state chemistry experience in their POSA definition, and for complexes being part of the pertinent art, is that the scope of the '659 patent claims does not exclude complexes of valsartan and sacubitril, and today it is understood to cover LCZ696 (a complex of valsartan and sacubitril). Op. Br. at 5; DFoF ¶ 9. This is hindsight. That the claims do not exclude complexes does not suggest that the pertinent art is solid-state chemistry or that a POSA would have known about complexes. The only example of a complex of valsartan and sacubitril cited by Dr. Steed was undisputedly invented years after the '659 patent priority date. PFoF ¶¶ 178, 202, 204.

Best Medical does not support Defendants' position. In *Best Medical*, the court determined that defining the POSA as having "formal computer programming experience" was not unreasonable where the claims expressly required using a computer and the specification was "replete with references to the invention being implemented on a computer." *See Best Medical*, 46 F.4th at 1353–54. In contrast to the facts of *Best Medical*, the '659 patent claims do not require valsartan and sacubitril to be present in the form of a complex (there is no claim element directed to non-covalently linking valsartan and sacubitril) and the specification is not "replete with references to" complexes (in fact, there are none). PFoF ¶¶ 166–171, 177, 179, 180, 183.

In sum, it is only with the Defendants' hindsight knowledge of LCZ696 (a complex of valsartan and sacubitril), which was first made after 2002, that Defendants identified solid-state

chemistry references as relevant to enablement of the '659 patent. There is nothing in the '659 patent or the remainder of the intrinsic record directed to making a complex of two active pharmaceutical ingredients that would lead a POSA to search for or consider such art, or that would require solid state chemistry experience.

2. *Under* Hogan, *the Court Should Not Consider Defendants' Facts Regarding a Later State of the Art*

Under *Hogan*, *Chiron*, and *U.S. Steel*, the post-2002 discovery of the first complex of valsartan and sacubitril (LCZ696) cannot be considered in the enablement analysis. *Supra* § III.A.1. Dr. Steed admitted that LCZ696 was first synthesized in 2006, years after 2002. PFoF ¶¶ 202,204. The discovery of LCZ696 was a change in the state of the art that occurred after 2002. PFoF ¶ 203. It is undisputed that as of the 2002 priority date, a POSA (under either definition) with the '659 patent in hand would not have known of or contemplated complexes of valsartan and sacubitril or foreseen that a complex of valsartan and sacubitril would exist. PFoF ¶¶ 181–183; Op. Br. at 29 (admitting "a POSA reviewing the specification as [of] the priority date would not have contemplated, foreseen, or envisioned such complexes"). The Court should disregard Defendants' post-2002 facts regarding a later state of the art related to complexes of valsartan and sacubitril. DFoF ¶¶ 87, 91–94, 109–117.[6]

3. *There Is No Evidence in the Record That Novartis's POSA Knew About Complexes in 2002*

Defendants incorrectly claim that all of the facts concerning enablement "are not in dispute" and "[t]his case is purely a legal dispute." Op. Br. at 2, 15–16. To the contrary, neither

[6] That Novartis claimed pharmaceutical compositions comprising the combination of valsartan and sacubitril in 2002, and thereafter discovered and filed patent applications claiming that separately innovative combination in the form of a complex in 2006 (Tr. 448:21–25 (Klibanov)), is consistent with the "ubiquitous" practice of patenting improvement and selection inventions. *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1340 (Fed. Cir. 2003).

Novartis nor Dr. Klibanov ever suggested, as Defendants allege (Op. Br. at 15; DFoF ¶ 90), that Novartis's POSA in 2002 would have known of "complexes, such as co-crystals and co-salts." PFoF ¶ 185; *contra* Op. Br. at 15. And Defendants have failed to prove by clear and convincing evidence that Novartis's POSA had such knowledge. PFoF ¶¶ 184–186.

Defendants' and Dr. Steed's sole reference that mentioned complexes as of 2002 is Aakeröy 1997 (JTX 254).[7] But Aakeröy 1997 was published in the solid-state chemistry journal *Acta Crystallographica*—an entirely different field of art from the '659 patent (treatment of hypertension and heart failure). PFoF ¶¶ 165–170, 179–184. Novartis's POSA would not have followed the literature on or been aware of solid-state chemistry references such as Aakeröy 1997. PFoF ¶ 184. Dr. Steed did not cite any evidence that complexes were nascent technology (as opposed to unknown technology) to Novartis's POSA as of 2002. PFoF ¶ 186.

Unlike Defendants' "full scope" enablement cases (*supra* § III.A.3), there is no evidence here that the pertinent art or the '659 patent specification contemplated complexes at all, much less complexes of valsartan and sacubitril. Rather, the facts here are analogous to the first application in *Chiron*, for which chimeric antibodies were "outside the bounds of the enablement requirement" as there was no evidence that such antibodies were known to or contemplated by a POSA as of the filing date. *Chiron*, 363 F.3d at 1254, *see also* 1251 (the "first publication that disclosed chimeric antibody technology did not appear until four months after [the filing date]"). And Defendants admit that *Chiron* is controlling Federal Circuit precedent that provides an enablement exception for unknown technology. Op. Br. at 26 n. 3. The '659 patent was not required to enable complexes

[7] Dr. Steed also relied on Ngilirabanga 2021 (JTX 240), a reference published 19 years after the 2002 priority date, but Dr. Steed did not explain how it was relevant to a POSA's knowledge as of 2002, or why Novartis's POSA would have been aware of it. *See* Tr. 187:9–18 (Steed); DFoF ¶ 83.

of valsartan and sacubitril, which would have been "impossible." *See Chiron*, 363 F.3d at 1254.

4. *Defendants Have Not Shown That Technology Relevant to Valsartan and Sacubitril Complexes Was Nascent, as Opposed to Unknown, to Defendants' POSA*

Defendants contend that complexes of valsartan and sacubitril would have been "a potential application of known technology" in 2002 because Defendants' POSA would have been aware that complexes (generally) existed. Op. Br. at 15, 22–24; DFoF ¶¶ 82, 84–86, 89–90, 95–98. But Defendants do not explain how knowledge of such complexes is relevant to complexes of valsartan and sacubitril. Defining the applicable technology here as any complexes is inconsistent with *Hogan*, which characterized the relevant technology as limited to just the technology needed to make the amorphous form of the specific claimed polymer, and not, for example, the technology needed to make amorphous solids generally. *See Hogan*, 559 F.2d at 597, 606 (the specification disclosed "the only then existing way to make" *the claimed polymer*). Defendants and Dr. Steed did not show that any technology potentially relevant to complexes of valsartan and sacubitril was nascent technology (as opposed to unknown technology) to Defendants' POSA as of 2002. PFoF ¶¶ 187–200. Whether complexes of valsartan and sacubitril were nascent technology which must be enabled is another factual issue. *Contra* Op. Br. 2, 15–16.

Defendants have not cited any credible evidence that Defendants' POSA in 2002 would have been aware of complexes for use in a pharmaceutical composition or for treating a condition or disease, much less a complex of two active pharmaceutical ingredients for treating hypertension or heart failure. Dr. Steed did not identify any such complex. PFoF ¶ 187. In fact, Dr. Steed testified that even years after 2002, pharmaceutical co-crystals were "new" and "unexplored," and the "possibility" of combining two active pharmaceutical ingredients in a single co-crystal was "interesting." PFoF ¶¶ 189–191. Dr. Steed's testimony that pharmaceutical complexes were known

to Defendants' POSA as of 2002 is unsubstantiated (*see* DFoF ¶¶ 83, 88, 95), and the Court should not credit it. PFoF ¶ 188; *see Cephalon, Inc. v. Watson Pharm., Inc.*, 707 F.3d 1330, 1338 (Fed. Cir. 2013) (an expert's "largely unsupported" testimony "carries little weight" and "cannot be enough to constitute clear and convincing evidence"); *Ashland Oil, Inc.*, 776 F.2d at 294–96. Dr. Steed only relied on Ngilirabanga 2021 (JTX 240) for his opinion that pharmaceutical complexes were known,[8] but Ngilirabanga 2021 was dated 19 years after 2002. Dr. Steed failed to explain how it was relevant to 2002 knowledge. *See* Tr. 187:9–18 (Steed); DFoF ¶ 83.

The Court should reject Defendants' attorney argument that in "[d]iscussing the application of co-crystals to the pharmaceutical industry," Aakeröy 1997 states "'we can expect much more interest in *this field* . . . from the pharmaceutical industry'" (DFoF ¶ 97 citing JTX 254 (Aakeröy 1997) at 580 (emphasis added)). No expert addressed this statement at trial, so there is no expert testimony that "this field" pertains to co-crystals as opposed to another topic addressed by Aakeröy 1997, which Dr. Steed admitted was generally directed to crystal engineering and not limited to co-crystals. PFoF ¶ 197; Tr. 218:21–24 (Steed) (stating Aakeröy 1997 "talked generally about the area of crystal engineering, including [*i.e.*, not solely] the formation of co-crystals"); JTX 254 (Aakeröy 1997 at 580 (cited statement appears in "3.4 Polymorphism" (pp. 579–81) not "2.2 Cocrystals" (pp. 572–73)).

As noted above, Defendants' and Dr. Steed's sole reference that mentioned complexes as of 2002 is Aakeröy 1997 (JTX 254). But Defendants failed to explain how Defendants' POSA

[8] Defendants and Dr. Steed cited two additional references published after 2002, Morissette 2004 (JTX 252) and Almarsson 2004 (JTX 234). Tr. 218:13–222:25 (Steed); DFoF ¶¶ 82–90, 95–98, 116–17. But Dr. Steed only testified that Morissette 2004 and Almarsson 2004 taught that co-crystals of drug and drug candidates were "new" and "unexplored," and prediction of packing structures was "not yet possible" by 2004, not that such co-crystals were known in 2002. Tr. 221:3–12, 222:4–12 (Steed).

would have identified Aakeröy 1997 as of 2002, or why it is relevant to complexes of valsartan and sacubitril or LCZ696.[9] Defendants and Dr. Steed also did not identify any example of a complex in Aakeröy 1997 (or elsewhere as of 2002) that was structurally similar to valsartan and sacubitril, or LCZ696, even though Aakeröy 1997 expressly stated that small changes in the structure of an active ingredient can dramatically affect co-crystallization. PFoF ¶¶ 192, 195, 196. Defendants have not identified any reason why Defendants' POSA would have searched for art such as Aakeröy 1997, and Dr. Steed did not identify any example of a complex in Aakeröy 1997 concerning ionic species even though valsartan and sacubitril are present in ionic forms in LCZ696. PFoF ¶¶ 193–194.

There is no evidence that Defendants' POSA would have foreseen that a complex of valsartan and sacubitril was something that could be explored or could come into existence in the future. Even after 2002, Defendants' POSA would not have known whether combining valsartan and sacubitril into a complex was even feasible. PFoF ¶¶ 200, 205. Dr. Steed recognized that it took a team of scientists at Novartis conducting over 1000 experiments to prepare a valsartan-sacubitril complex, and they did not know whether this was feasible before LCZ696 was first prepared. PFoF ¶¶ 204, 206–210.

Accordingly, the '659 patent was enabled when it was filed in 2002, and this ends the enablement inquiry. *Hogan*, 559 F.2d at 605. To avoid any doubt, Novartis is not arguing, as Defendants suggest, that complexes of valsartan and sacubitril need not be enabled "simply because the patentee failed to. . . practice [them]" (Op. Br. at 22–23). Rather, complexes of valsartan and sacubitril need not be enabled because the undisputed evidence proves that they were

[9] Defendants frame the issue here as whether the '659 patent must enable a "range of [complex] embodiments" (Op. Br. at 1, 15, 17, 27), but there is only evidence in the record of one such complex that is known and in existence today (LCZ696). PFoF ¶ 178.

not known or contemplated as of January 2002, and Defendants have not shown that the relevant technology was nascent technology (as opposed to unknown technology) to Defendants' POSA in 2002. Defendants have failed to provide clear and convincing evidence of non-enablement.

IV. DEFENDANTS HAVE FAILED TO PROVE LACK OF WRITTEN DESCRIPTION

Written description is "judged from the perspective of [a POSA] as of the relevant filing date" based on "an objective inquiry into the four corners of the specification." *Immunex Corp. v. Sandoz Inc.*, 964 F.3d 1049, 1063 (Fed. Cir. 2020). For a genus claim, the written description requirement can be satisfied by the "disclosure of . . . structural features common to the members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1350 (Fed. Cir. 2010) (en banc) (citation omitted). "[A]n adequate written description requires a precise definition, such as by structure, formula, chemical name, physical properties, or other properties, of species falling within the genus sufficient to distinguish the genus from other materials." *Id.*; *Pfizer Inc. v. Teva Pharm. USA, Inc.*, 555 F. App'x 961, 968 (Fed. Cir. 2014) ("[A]n application satisfies the written description requirement when it details 'relevant identifying characteristics' such that the [claimed] compound can be distinguished from other compounds.") (citation omitted). Adequate written description of a genus claim under *Ariad's* common structural features test thus does not require "actual possession" of every species of that genus, as Defendants suggest (Op. Br. 29–30).

The '659 patent satisfies the written description requirement by disclosing valsartan and sacubitril—the structural features (*i.e.*, chemical names and/or chemical formulas) common to the members of the claimed genus of the pharmaceutical composition containing the valsartan and sacubitril combination. *Ariad*, 598 F.3d at 1350. Specifically, the patent identifies, in structural terms, the claimed combination of valsartan and sacubitril. PFoF ¶¶ 213–214, 217–218.

Defendants do not dispute this. PFoF ¶¶ 213–214, 218. These chemical names provide a precise definition that allows a POSA to readily visualize or recognize embodiments falling within the scope of the claim and to distinguish combinations falling within the scope of the claim (such as physical mixtures or complexes of valsartan and sacubitril) from other combinations (such as combinations that do not include one or both of valsartan and sacubitril). PFoF ¶¶ 172–173, 215–216, 219–220; *Ariad*, 598 F.3d 1350; *Pfizer Inc.*, 555 F. App'x at 968.

Non-covalent linkages in a valsartan and sacubitril complex are not claim limitations or features that are common to all members of the claimed genus. PFoF ¶¶ 170–174, 221. For example, physical mixtures of the individual components would not have that feature despite such physical mixtures being within the scope of the claim. PFoF ¶ 221. Nor do these non-covalent linkage features distinguish between the claimed combination and subject matter not covered by the claims. PFoF ¶ 221. Thus, *Ariad* does not require the specification to disclose non-covalent linkages in a valsartan and sacubitril complex.

Defendants allege that *Chiron* and *Boston Scientific* show that the '659 patent lacked adequate written description because "Novartis did not have actual possession" of complexes of valsartan and sacubitril. Op. Br. 30. To the contrary, *Chiron* involved claims with functional (not structural) language and is therefore inapposite to the written description inquiry under *Ariad*'s common structural features test (not addressed in *Chiron*). *Chiron*, 363 F.3d at 1250 (claims to "[a] monoclonal antibody that binds to" a cancer antigen). In *Boston Scientific*, the applicant failed to disclose structural features common to the members of the claimed genus sufficient to distinguish it from species falling outside the genus. *Boston Sci. Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1364 (Fed. Cir. 2011) (finding the specification "contain[ed] virtually no information regarding [the claimed] analogs of rapamycin" and only "vague[]" guidance to determine whether

a compound fell within the claim). As explained above, that is not the case here.

The '659 patent satisfies the written description requirement by describing structural features common to the claimed genus. Thus, the later discovery of LCZ696 after the filing date and *Ariad*'s alternative representative species test (*Ariad*, 598 F.3d at 1350) are not relevant and LCZ696 does not need to be described. *Contra* DFoF ¶ 125.

V. DEFENDANTS HAVE FAILED TO PROVE INDEFINITENESS

To satisfy the definiteness requirement, a claim, "viewed in light of the specification and prosecution history, must 'inform those skilled in the art about the scope of the invention with reasonable certainty.'" *Nevro Corp. v. Boston Sci. Corp.*, 955 F.3d 35, 38–39 (Fed. Cir. 2020) (*quoting Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 910 (2014)). The '659 patent claims, read in view of the repeated and consistent references to weight amounts and dosages in the specification and file history, clearly inform a POSA with "reasonable certainty" that the claimed ratio is a weight ratio. PFoF ¶¶ 222–228; *see Nevro*, 955 F.3d at 38–39. Defendants implicitly acknowledge the weakness of their indefiniteness theory by only including it in a footnote without explanation. Op. Br. at 30 n. 4. Defendants' only case (*Teva*) was decided based on completely different facts. *See Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 789 F.3d 1335, 1343–45 (Fed. Cir. 2015) (the patent applicant defined the disputed term in different ways to overcome separate indefiniteness rejections during prosecution of two related patents). Defendants have not shown by clear and convincing evidence that the claims are invalid for indefiniteness.

VI. CONCLUSION

Defendants have failed to present clear and convincing evidence to rebut the presumption that the asserted claims of the '659 patent are valid, and therefore Novartis respectfully asks the Court to reject each of the Defendants' validity challenges.

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