IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

In re Entresto (Sacubitril/Valsartan) Patent Litigation	MDL No. 20-2930-RGA C.A. Nos. 19-1979-RGA 19-2021-RGA 19-2053-RGA

TRIAL OPINION

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ANDREWS, U.S. DISTRICT JUDGE:

This case is part of the multi-district litigation of patent infringement claims regarding Entresto® (sacubitril/valsartan). *In re Entresto (Sacubitril/Valsartan) Patent Litigation*, C.A. No. 20-md-02930 ("*In re Entresto*"). Novartis brought this action against Defendants for infringement of U.S. Patent 8,877,938 (the "'938 Patent"), 9,388,134 (the "'134 Patent"), 8,101,659 (the "'659 Patent") and 8,796,331 (the "'331 Patent"). Only the '659 Patent is at issue in this opinion.

The parties dispute whether claims 1–4 of the '659 Patent (collectively, "the asserted claims") are invalid for obviousness, lack of written description, non-enablement, and indefiniteness. On September 12, 2022, I held a three-day bench trial.[1] (D.I. 595–597).[2]

I have considered the parties' post-trial submissions (D.I 599, 600, 618, 619, 620). Having considered the documentary evidence and testimony, I make the following findings of fact and conclusions of law pursuant to Federal Rule of Civil Procedure 52(a).

I. BACKGROUND

Novartis is the holder of New Drug Application ("NDA") No. 207620 for Entresto®, a tablet containing the active ingredients sacubitril[3] and valsartan.[4] (D.I. 521-1, Ex. 1 at 5–6). The FDA has approved Entresto® "to reduce the risk of cardiovascular death and hospitalization for

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[1] The '331 Patent was also asserted in that trial. (D.I. 521-1, Ex. 1 at 11; D.I. 537). The '331 Patent's expiration date is January 14, 2023, and the '331 Patent is subject to pediatric exclusivity until July 14, 2023. (D.I. 601 at 3). The parties agreed that I need not reach a decision regarding the validity of that patent. (*Id.*). I held separate trials addressing the '938 Patent and the '134 Patent. (D.I. 604–607 (infringement), D.I. 608–609 (invalidity)).

[2] Unless otherwise specified, the docket referred to is C.A. No. 1:19-cv-01979.

[3] The chemical name for sacubitril is N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester. (D.I. 521-1, Ex. 1 at 6). Sacubitrilat—also referred to by the chemical name (2R,4S)-5-biphenyl-4-yl-4- (3-carboxypropionyl amino)-2-methyl-pentanoic acid—is the active metabolite of the prodrug sacubitril. (*Id.*). The term "sacubitril" herein includes both sacubitril and sacubitrilat unless otherwise specified.

[4] The chemical name for valsartan is (S)—N-(1-carboxy-2-methylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl-methyl]amine. (D.I. 521-1, Ex. 1 at 6).

heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction," "for treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older," and "to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure." (*Id.*).

The '659 Patent is listed in the FDA's Orange Book for Entresto®. (*Id.* at 11). The '659 Patent's undisputed priority date is January 17, 2002. (*Id.* at 11). The patent generally relates to compositions of valsartan and sacubitril and the use of such compositions to treat hypertension and heart failure. Defendants submitted Abbreviated New Drug Application ("ANDAs") for approval to market generic versions of Entresto®. (*Id.* at 7–11). Plaintiff initiated this lawsuit, asserting infringement of claims 1–4 of the '659 Patent ("the asserted claims") against all Defendants. (*Id.* at 2, 11). Defendants stipulated to infringement of the asserted claims (*id.* at 17–18), but Defendants assert that the claims are invalid.

II. ASSERTED CLAIMS

The claims at issue are claims 1–4 of the '659 Patent ("the asserted claims"). (D.I. 521-1, Ex. 1 at 11).

Claim 1 reads:

1. A pharmaceutical composition comprising:

   (i) the AT 1-antagonist valsartan or a pharmaceutically acceptable salt thereof;

   (ii) the NEP inhibitor N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester or (2R,4S)-5-biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or a pharmaceutically acceptable salt thereof; and

   (iii) a pharmaceutically acceptable carrier;

   wherein said (i) AT 1-antagonist valsartan or pharmaceutically acceptable salt thereof and said (ii) NEP inhibitor N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester or (2R,4S)-

> 5-biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salt thereof, are administered in combination in about a 1:1 ratio.

(*Id.* at 11–12).

Claim 2 depends from claim 1 and reads:

> 2. The pharmaceutical composition of claim 1, wherein said (i) AT 1-antagonist valsartan or a pharmaceutically acceptable salt thereof and said (ii) NEP inhibitor N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester or (2R,4S)-5-biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salt thereof are administered in amounts effective to treat hypertension or heart failure.

(*Id.* at 12).

Claim 3 depends from claim 1 and reads:

> 3. The pharmaceutical composition of claim 1 wherein (ii) said NEP inhibitor is N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester.

(*Id.*).

Claim 4 depends from claim 3 and reads:

> 4. The pharmaceutical composition of claim 3 in the form of a capsule or tablet.

(*Id.*).

III. OBVIOUSNESS

A. Legal Standard

A patent claim is invalid as obvious under 35 U.S.C. § 103 "if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." 35 U.S.C. § 103; *see also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406-07 (2007). "As patents are presumed valid, a defendant bears the burden of proving invalidity by clear and convincing evidence." *Shire, LLC v. Amneal Pharms.*,

LLC, 802 F.3d 1301, 1306 (Fed. Cir. 2015) (citations omitted). "Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined." *KSR*, 550 U.S. at 406 (internal citation and quotation marks omitted).

A court is required to consider secondary considerations, or objective indicia of nonobviousness, before reaching an obviousness determination, as a "check against hindsight bias." *See In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1078-79 (Fed. Cir. 2012). "Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17–18 (1966).

B. Findings of Fact

1. Level of Ordinary Skill in the Art

The parties dispute whether a person of ordinary skill in the art ("POSA") would have knowledge and experience in solid-state chemistry. (*See* D.I. 599 at 5; D.I. 600 at 2–3; D.I. 618 at 35–38; D.I. 619 at 30–31; D.I. 620 at 11). The parties do not argue that the outcome of the obviousness analysis would change depending on whose position I adopt. Instead, the parties assert that their dispute is relevant to the enablement and written description analyses. (*See, e.g.*, D.I. 619 at 30–31 (framing POSA definition as § 112 issue); D.I. 620 at 10 (same)). Accordingly, I discuss the parties' disagreement, and my conclusions, in that portion of this opinion. *See infra* Section IV.A.2.

Ultimately, I think that Plaintiff's definition of a POSA is the correct definition. I therefore conclude that a POSA with respect to the '659 Patent is "a medical doctor or Ph.D. in medicinal chemistry or a related field who is interested in developing new drugs for heart failure and hypertension, and would not have had experience, familiarity, or interest in solid-state chemistry." (D.I. 619 at 30–31; Tr. at 47:17–23 (Dr. Fintel); *Id.* at 279:24–280:8 (Dr. Spinale); *Id.* at 399:8–21, 401:8–402:9 (Dr. Klibanov)).

2. Scope and Content of the Prior Art

a. Background

i. Heart Failure and Hypertension

Hypertension is "abnormally high arterial blood pressure"—a disease of the arteries. (Tr. at 281:4–10 (Dr. Spinale); JTX-133 at 308). Heart failure is a "condition in which the heart is unable to pump blood at an adequate rate or an adequate volume"—a disease of the heart muscle. (Tr. at 11–14 (Dr. Spinale); JTX-133 at 278). I agree with Plaintiff that, in 2002, a POSA understood these disease states to be distinct from each other. (D.I. 619 at 2; Tr. at 282:4–10 (Dr. Spinale)). Hypertension and heart failure were studied using different research methodologies (Tr. at 282:21–283:9 (Dr. Spinale)); entailed different goals and guidelines with respect to treatment (*id.* at 284:6–10 (Dr. Spinale)); and were sometimes treated using drugs that ameliorate one condition, but not the other. (*Id.* at 283:22–284:5 (Dr. Spinale)).

I also agree with Defendants, however, that a POSA would also have understood that these disease states are related to each other in significant ways. (*See* D.I. 600 at 15). Hypertension is the most common clinical condition closely associated with and leading to heart failure. (Tr. at 50:19–51:8 (Dr. Fintel); JTX-211 at 1557). Over the decades prior to the priority date, it was known that controlling blood pressure helps to prevent heart failure (*id.* at 51:9–22 (Dr. Fintel)).

Multiple drug categories developed to treat hypertension were prescribed to treat heart failure as well. (*Id.* at 52:5–24 (Dr. Fintel)).

ii. Combination Treatment for Heart Failure and Hypertension

Defendants argue that, in 2002, combination treatment for hypertension and heart failure was standard. (D.I. 600 at 17). Plaintiff argues to the contrary. (D.I. 619 at 3–4). Plaintiff cites Dr. Spinale's testimony that certain combination treatments could be ineffective or result in adverse effects. (Tr. 304:4–17 (Dr. Spinale)). Dr. Spinale admitted, however, that combining drugs from different classes to treat hypertension (Tr. at 378:6–10 (Dr. Spinale)) and heart failure (*id.* at 378:2–5 (Dr. Spinale)) was standard.[5] Thus, I generally agree with Defendants that combination treatment was established in the field with respect to both hypertension and heart failure.

The size of the universe of potential drugs that a person skilled in the art would encounter when seeking an effective combination is relevant to the obviousness analysis. *See In re Kubin,* 561 F.3d 1351, 1361 (Fed. Cir. 2009). The more potentialities, the less likely that a particular combination is obvious. *Id.* The fewer potentialities, the more likely that a particular combination is obvious. *Id.*

Plaintiff argues that the possibilities were vast in number. (D.I. 619 at 2). I agree. If a POSA were interested in pursuing a new treatment for hypertension or heart failure as of 2002, there was a myriad of potential combinations that could be considered, including both clinically approved drugs and those that were the subject of clinical research. (Tr. at 307:16–308:12 (Dr. Spinale); *see*

[5] Plaintiff emphasizes that neither Dr. Fintel nor Dr. Spinale testified that it was standard to treat either condition with a combination that included drugs that were not FDA-approved for a condition. (D.I. 619 at 3–4). Plaintiff does not point to any part of the trial transcript in which Dr. Fintel or Dr. Spinale were asked to opine on this subject, and I have not independently located any such testimony. Dr. Spinale testified to combination treatment, generally. (Tr. at 378:2–10 (Dr. Spinale)). Thus, I am not convinced by Plaintiff's argument with respect to FDA approval.

also id. at 52:5–24 (Dr. Fintel (listing drug categories used to treat hypertension and heart failure)); PTX-1017 (FDA-approved products to treat hypertension included multiple ACE inhibitors, alpha-blockers, ARBs, beta-blockers, calcium antagonists, diuretics, and direct vasodilators); PTX-1018 (FDA-approved products to treat heart failure included multiple ACE inhibitors, beta-blockers, diuretics, and positive inotropic agents)). Thus, this factor weighs against a finding of obviousness.

Defendants do not dispute the number of possibilities at play here. Defendants maintain, however, that good reasons existed for a POSA to pursue the combination of valsartan—an ARB—and sacubitril—a NEPi—for heart failure and hypertension. According to Defendants, a POSA would have pursued this combination because: (1) the ARB-NEPi combination was known as of the priority date and was reported to have synergistic effects for the treatment of both conditions (D.I. 599 at 7–8); (2) ACEi-NEPi combinations were known, and the prior art suggested that replacing the ACEi with an ARB would reduce side effects associated with the ACEi (*id.*); (3) the prior art suggested that an ARB-NEPi combination could unmask the benefits of the NEPi (*id.*); (4) valsartan was a preferred ARB for heart failure and hypertension (*id.* at 8–9); and (5) sacubitril was a preferred NEPi for heart failure and hypertension (*id.* at 9–10). I address these arguments in detail below.

b. Angiotensin-Converting Enzyme Inhibitors (ACEis)

As of 2002, ACEis were used to treat hypertension and heart failure. (Tr. at 52:5–24 (Dr. Fintel)). Plaintiff contends that ACEis were the "gold standard of heart failure therapy" (D.I. 619 at 17), a characterization fairly supported by Dr. Spinale's testimony (*e.g.*, Tr. at 303:21–24) and by standard-of-care guidelines from the American College of Cardiology and the American Heart Association. (*See* JTX-366 (2001 Guidelines) at 3002 (giving ACEis a Class I recommendation—

the strongest possible recommendation—for treatment of symptomatic left ventricular systolic dysfunction)).

In 2002, ACEis were understood to treat hypertension and heart failure in the following ways. Angiotensin-converting enzyme (ACE) converts the protein angiotensin I into angiotensin II, which causes vasoconstriction and thereby raises blood pressure. (Tr. at 57:12–22 (Dr. Fintel)). ACEis block this conversion, thereby lowering blood pressure. (*Id.* at 57:14–58:12 (Dr. Fintel)). ACEis also prevent ACE from breaking down bradykinin, which can lead to an accumulation of bradykinin. (*Id.* at 59:12–18 (Dr. Fintel)). Bradykinin accumulation was believed to contribute to the beneficial effects of ACEis. (*Id.* at 131:1–131:2 (Dr. Fintel); *id.* at 315:23–316:17 (Dr. Spinale)).

Defendants assert that the accumulation of bradykinin can also lead to side effects, including a serious condition called angioedema. (D.I. 600 at 16; Tr. at 59, 12–23 (Dr. Fintel)). Plaintiff responds that a POSA would not have understood this, as the cause of angioedema was unknown as of 2002, and thus the connection between bradykinin accumulation and angioedema was inconclusive. (D.I. 619 at 17 (citing Tr. at 313:12–314:7 (Dr. Spinale); JTX-57; JTX-194)). I would not go so far. The evidence that Plaintiff cites indicates that POSA would have understood that bradykinin accumulation may play a role in angioedema. (*See, e.g.*, JTX-194 at 172 ("A great part of all reviewed reports suggest a relationship between … angioedema and increased levels of … bradykinin.")).

In any event, I think that, even absent a clear understanding of the role of bradykinin, a POSA would understand that ACEis are associated with angioedema. While I credit Dr. Spinale's testimony that ACEis were well tolerated, with low estimated incidence of angioedema (Tr. at 312:20–313:10 (citing JTX-138, JTX-151)), the record reflects that a POSA would have been

aware that angioedema is a serious possible adverse effect of ACEi therapy, and that this was a problem that persons skilled in the art were seeking to solve. (*See, e.g.*, JTX-194 at 172 ("The incidence of angioedema is low … but can be considered as a potentially life-threatening adverse effect of ACE inhibitor therapy. … The estimated incidence is quite underestimated.")).

c. Angiotensin Receptor Blockers (ARBs) and Valsartan

ARBs were developed in the 1990s. (Tr. at 60:15–17 (Dr. Fintel)). ARBs act by blocking the interaction of angiotensin II with the AT_1 receptor, which ultimately decreases blood pressure. (*Id.* at 60:15–67:1 (Dr. Fintel)). In 1995, the forerunner to Novartis, Ciba-Geigy, was issued U.S. Patent No. 5,399,578 ("the '578 Patent"). (JTX-23). That patent disclosed and claimed the use of the ARB valsartan for hypertension and for "cardiac insufficiency," which a POSA would have understood to be heart failure. (Tr. at 76:3–9 (Dr. Fintel); JTX-23). In 1996, the FDA approved valsartan (Diovan®) for hypertension. (JTX-67 (Diovan® Label)). By 2002, there was "great interest" in studying ARBs for use in heart failure treatment. (Tr. at 376:16–20 (Dr. Spinale)). The emerging data was promising; for example, the 2001 Val-HeFT clinical trial concluded that the ARB valsartan "significantly reduces the combined end point of mortality and morbidity and improves clinical signs and symptoms in patients with heart failure." (JTX-60 at 1667). I credit Dr. Fintel's testimony that such studies generated "buzz" among cardiologists, who used ARBs increasingly often to treat heart failure. (Tr. at 74:21–75:5; *see also* DTX-686 at 2:12–20 (stating that ARBs can be used for the treatment of congestive heart failure)).

A central disagreement concerns angioedema. Defendants assert that ARBs do not lead to bradykinin accumulation and therefore lack bradykinin-induced side effects, such as angioedema, that were associated with ACEis. (D.I. 600 at 17 (citing Tr. at 61:8–13 (Dr. Fintel))). I don't think this characterization is entirely accurate; as Plaintiff points out (D.I. 618 at 18), it was known that

ARBs could potentially cause angioedema. (Tr. at 315:9–16 (Dr. Spinale); PTX-198 at 2167). ARBs were, however, associated with a lower relative incidence of angioedema. (JTX-151 at 831; JTX-164 at 80). Defendants contend that doctors preferred ARBs to ACEis on this basis. (D.I. 620 at 3). I do not think that ARBs were poised to surpass ACEis altogether—as Plaintiff says (D.I. 619 at 17), ACEis remained the "gold standard" in 2002. (*See* JTX-366 at 3002). But I think that a POSA would have viewed a reduced risk of angioedema as one of the benefits of the ARB class. (*See* JTX-366 at 3002 (recommending ARBs in patients who cannot be given an ACE inhibitor because of cough or angioedema)).

Six ARBs were FDA-approved for hypertension in 2002. (PTX-1017 (including, e.g., irbesartan and valsartan)). Defendants argue that valsartan was a preferred ARB for heart failure and hypertension.[6] (D.I. 600 at 18–20). Defendants assert that three properties distinguish valsartan from the other ARBs: potency, selectivity, and liver enzyme affinity. For potency, Defendants rely on Shetty (JTX-169), which investigated the relative potency of four ARBs and reported that valsartan was, numerically, the most potent. (*Id.* at 185). But as Plaintiff notes (D.I. 619 at 14–15), the reported difference in potency between valsartan and the second-most-potent ARB, irbesartan, was not statistically significant. (*Id.*). Furthermore, I agree with Plaintiff (*id.* at 15) that Defendants did not provide clear and convincing evidence linking potency to any clinical advantage. Thus, I do not think that Defendants' potency argument is particularly persuasive.

[6] Counter to Defendants' argument (e.g., D.I. 599 at 8), I don't think that U.S. Patent No. 6,211,217 ("the '217 Patent," which identifies Dr. Spinale as an inventor) (DTX-686) confirms that valsartan was a preferred ARB for these conditions. Defendants say that the '217 Patent disclosed the use of valsartan to treat hypertension and heart failure. (D.I. 600 at 19). I disagree. That patent 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. (DTX-686 at Abstract, 8:66–67).

Neither am I convinced by Defendants' argument regarding valsartan's selectivity. Defendants rely on Malacco (JTX-118), which compared valsartan and irbesartan and reported that valsartan is more selective for the AT_1 receptor as opposed to the AT_2 receptor. (*Id.* at 790). This is a clinically advantageous property, say Defendants, because the target of an ARB is the AT_1 receptor—the receptor responsible for, e.g., the control of blood pressure—whereas the AT_2 receptor counteracts the effects of the AT_1 receptor. (D.I. 600 at 19 (citing Tr. at 66:21–67:13 (Dr. Fintel); JTX-118 at 795)). Maybe so. But as Plaintiff points out (D.I. 618 at 16), Malacco taught that this difference in selectivity did not appear to result in any differences between irbesartan and valsartan with respect to the magnitude and duration of antihypertensive efficacy. (JTX-118 at 790). The clinical relevance of Malacco's selectivity finding is therefore unclear.

As for liver enzyme affinity, Defendants point to Taavitsainen (JTX-218), which investigated potential interactions of five ARBs with various drug-metabolizing enzymes. (*Id.* at 135). Dr. Fintel explained that lower rates of interaction are clinically advantageous, as lower interaction rates suggest a lower potential for drug-drug interactions. (Tr. at 70:6–13; JTX-218 at 135). Taavitsainen reported that, compared to losartan and irbesartan, valsartan demonstrates a 5- to 30-fold lower rate of interaction with the CYP2C9 enzyme. (*Id.* at 137 (concluding that losartan and irbesartan are "the most obvious candidates to cause potentially significant interactions" with respect to this enzyme)). Counter to Defendants' assertions (D.I. 600 at 13), I do not think that Taavitsainen broadly teaches that valsartan has a lower potential for drug-drug interactions as compared to other ARBs. Indeed, it is unclear to me what a POSA would conclude from Taavitsainen, as Defendants decline to discuss Taavitsainen's findings with respect to the other ARBs and enzymes investigated.

In sum, I agree with Plaintiff (D.I. 618 at 16) that Defendants have failed to show that a POSA would view valsartan as a "preferred ARB" by virtue of its potency, selectivity, or liver enzyme affinity. There was no clear hierarchy of ARBs. Indeed, as Plaintiff points out (D.I. 619 at 16), when valsartan and irbesartan were explicitly compared to each other in a clinical context, valsartan ranked beneath irbesartan; for example, Mancia (JTX-119) taught that irbesartan demonstrated superior results with respect to blood pressure reduction in hypertension patients. (JTX-119; Tr. at 301:19–23 (Dr. Spinale)).

d. Neutral Endopeptidase Inhibitors (NEPis) and Sacubitril

NEPis are another class of agent that can result in vasodilation. (Tr. at 62:8–17 (Dr. Fintel)). In 2002, the universe of candidate NEPis was large. Over 100 NEPis had been identified, and approximately 50 NEPis had been studied in animal models and demonstrated preclinical activity. (Tr. at 440:10–441:6 (Dr. Klibanov); PTX-1021 (summary exhibit of NEPis disclosed in the prior art); Tr. at 297:21–298:9 (Dr. Spinale); *id.* at 126:23–127:1 (Dr. Fintel)). One such NEPi was sacubitril. Sacubitril had not, as of 2002, been administered to humans. (Tr. at 125:22–126:6 (Dr. Fintel)).

Defendants argue that sacubitril was a preferred NEPi for heart failure and hypertension. (D.I. 600 at 20; D.I. 599 at 9–10). In support of this position, Dr. Fintel relied on two prior art references: U.S. Patent No. 5,217,996 ("the '996 Patent") (JTX-362) and Ksander (JTX-352). (Tr. at 126:7–9). The '996 Patent was filed in 1992 by Ciba-Geigy. (Tr. at 91:2–4 (Dr. Fintel); *Id.* at 299:20–24 (Dr. Spinale)). That patent disclosed the NEPi sacubitril and its recommended doses, claimed the use of sacubitril for "treating cardiovascular disorders," and explained that such disorders include hypertension and heart failure. (JTX-362 at 1:22–28, 11:7–12, claim 11). It did

not compare sacubitril to the other NEPis that were known at the time. (Tr. at 297:21–298:9 (Dr. Spinale)).

Ksander disclosed Ciba-Geigy's efforts "to identify novel NEP inhibitors with superior pharmacologic properties" compared to candidate NEPis that had already been studied. (JTX-352 at 1689). To this end, Ksander synthesized and evaluated 31 NEPis and reported that, of these compounds, sacubitrilat[7] was the most potent. (*Id.* at 1692). Ksander also reported that sacubitrilat's potency is similar to that of two known NEPis (thiorphan and CGS 24,592). (Tr. at 441:8–442:15 (Dr. Klibanov); JTX-352 at 1693). Ksander cited an article concerning the hypertensive and renal activity of another known NEPi—SQ 28,603 (JTX-352 at 1689, 1699), which is the NEPi used in the single ARB-NEPi combination disclosed in the prior art. *See infra* Section III.B.2.e.i. This article was one of dozens of references that Ksander cited. (*See* JTX-352 at 1699–700). Neither Dr. Fintel nor Dr. Spinale testified that SQ 28,603 was one of the NEPis that Ksander compared to sacubitril or sacubitriliat, nor have the parties cited any prior art suggesting that sacubitril or sacubitrilat is more potent than SQ 28,603.

In 1997, Novartis abandoned the '996 Patent, and no one pursued further research with sacubitril between 1997 and 2002. (Tr. at 300:12–18 (Dr. Spinale)). As of 2002, sacubitril had never been administered to humans or tested in an animal model of hypertension and heart failure. (Tr. at 125:22–126:6 (Dr. Fintel)). Other NEPis, however, had been clinically tested in hypertension and heart failure patients, and the results were discouraging. For example, Cleland (JTX-56) reported that the NEPi ecadotril failed to improve heart failure symptoms, and Asher (JTX-38) discussed similarly disappointing results with respect to NEPis' effectiveness as a

[7] Sacubitrilat is the claimed active metabolite of sacubitril into which sacubitril converts *in vivo*. (Tr. at 90:2–11 (Dr. Fintel); D.I. 521-1, Ex. 1 at 6).

monotherapy for hypertension. (*See id.* at 387; Tr. 299:25–300:11 (Dr. Spinale)). By 2002, a POSA would have understood that NEPis had not performed well in clinical trials with respect to hypertension and heart failure treatment. (Tr. at 92:13–21, 94:2–16 (Dr. Fintel); JTX-352 at 1689).

The parties dispute a POSA's interpretation of these disappointing results. Defendants say that a POSA would have understood that the beneficial effects of NEPis might have been masked by their negative effect of increasing angiotensin II levels. (D.I. 600 at 10). Defendants rely on Cleland (JTX-56), which disclosed a clinical study in which the NEPi ecadotril failed to improve symptoms for heart failure patients who were also receiving ACEis and conventional diuretic therapy. (*Id.* at 1657–58). Defendants' theory is that, because ACEis have no effect on already-existing angiotensin II, the negative activity of ecadotril (that is, increased angiotensin II) obscured ecadotril's positive activity. (*See* D.I. 600 at 9–10; D.I. 620 at 7–8). I do not think that a POSA would have understood this from Cleland. I credit Dr. Spinale's testimony that compelling prior art suggested that NEPis reduce, rather than increase, angiotensin II levels, and that theories to the contrary were purely theoretical. (Tr. at 308:21–309:12 (citing JTX-91; JTX-92)). Cleland does not suggest otherwise; indeed, Defendants admit that Cleland reported that angiotensin levels did not increase after patients were administered the NEPi. (D.I. 600 at 10; JTX-56 at 1658). I am therefore unmoved by Defendants' argument that Cleland would motivate a POSA to unmask the benefits of NEPis by combining a NEPi with an ARB, which blocks the action of already-existing angiotensin II. (D.I. 600 at 10).

e. Combination Strategies

NEP inhibition, although largely ineffective as a standalone treatment for heart failure and hypertension, showed more promise when combined with other mechanisms of action. I discuss these combinations below.

i. ARB plus NEPi

Defendants rely on a single ARB-NEPi combination disclosed in the prior art: that of the ARB irbesartan and the NEPi SQ 28,603. This combination was disclosed in Bristol-Myers Squibb's ("BMS's") European Patent Application No. 726,072 ("EP '072") (JTX-368), which reports data in a heart failure animal model (the cardiomyopathic hamster in Example 1) and a hypertension animal model (the 1K1C dog in Example 2). (D.I. 600 at 27; D.I. 619 at 6). Trippodo (JTX-369) discloses the same experiment as Example 1. (D.I. 619 at 6). The parties agree that, in the hypertensive dog experiment disclosed in EP '072 Example 2, the ARB-NEPi combination did not result in a statistically significant effect on the main response variable—mean arterial pressure, i.e., the average blood pressure in the arteries (Tr. at 118:6–8 (Dr. Fintel))—as compared to vehicle alone. (D.I. 619 at 8; D.I. 600 at 18; Tr. at 119:12–16 (Dr. Fintel)). The focus of the parties' disagreement is the cardiomyopathic hamster experiment disclosed by EP '072 Example 1/Trippodo. Both parties agree that EP '072 Example 1/Trippodo disclosed that an ARB-NEPi combination caused decreases in left ventricular end diastolic pressure ("LVEDP") and left ventricular systolic pressure ("LVSP") that were "synergistic"—i.e., greater than the sum of the decreases produced by each drug alone. (D.I. 619 at 7–8; D.I. 600 at 8). What the parties dispute is whether a POSA would view these findings as favorable with respect to the treatment of hypertension and heart failure.

I begin with hypertension. As mentioned above, Defendants acknowledge that EP '072 Example 2 reported a "lack of a statistically significant difference in the hypertensive dogs" with respect to lowering blood pressure.[8] (D.I. 600 at 18). Defendants argue, however, that a POSA

[8] The parties do not dispute that a POSA would have known that lowering blood pressure treats hypertension. (D.I. 600 at 15; *see* D.I. 619 at 8).

would nevertheless have concluded that ARB-NEPi combination is promising for hypertension, given the success of the cardiomyopathic hamster experiment disclosed in EP '072 Example 1/Trippodo. (D.I. 599 at 7 (citing Dr. Fintel's testimony that "the demonstration [of success] in at least one model, in this case the hamster heart failure model … would be very encouraging." Tr. at 134:13–19)).

Plaintiff disagrees. First, Plaintiff challenges the idea that the reported reductions in LVEDP and LVSP are sufficient to demonstrate that the ARB-NEPi combination had antihypertensive effects. (D.I. 618 at 4–5). Plaintiff's primary argument is that a POSA would have understood that the LVSP measure reported in EP '072 Example 1/Trippodo—i.e., peak LVSP—has no bearing on blood pressure. (*Id.* at 5). According to Dr. Spinale, peak LVSP reflects the heart's "ejection performance, or how much blood has been propelled out into the body," which is different from blood pressure. (Tr. at 293:12–25). Dr. Spinale also stated that LVEDP measurements are irrelevant to blood pressure. (*Id.* at 294:3–10). I am more convinced by Defendants' evidence that a POSA would have considered reductions in LVEDP and LVSP to be antihypertensive. Dr. Fintel explained that reducing LVSP reduces aortic pressure, thereby reducing systolic blood pressure (*id.* at 83:4–8), and that reducing LVEDP treats hypertension for "preload dependent" patents by lowering ventricular output. (*Id.* at 82:7–9). I find Dr. Fintel's testimony persuasive.

Second, Plaintiff disputes the extent to which a POSA would be able to draw conclusions about hypertension treatment from EP '072 Example 1/Trippodo, given the nature of the animal model used in that experiment. (D.I. 618 at 4–6). Plaintiff notes that "the cardiomyopathic hamster model is not a model of hypertension" (*id.* at 4)—a fact that Defendants do not dispute. (D.I. 600 at 18). Plaintiff argues that, consequently, the EP '072 Example 1/Trippodo findings are irrelevant

to hypertension, as "to answer the question of whether a combination treats hypertension, a POSA would need to test it in a hypertension model." (D.I. 618 at 6). Plaintiff emphasizes the distinctions between heart failure and hypertension and argues that, because of these differences, "a POSA would not have considered heart failure data relevant to treating hypertension." (*Id.*).

Dr. Fintel acknowledged that the combination in EP '072 Example 1/Trippodo was "not treating the clinical problem of hypertension because [cardiomyopathic hamsters] were not hypertensive animals." (Tr. at 120:14–16). Dr. Fintel also admitted that, to answer the question of whether a combination treats hypertension, a POSA would need to test the combination in a hypertensive animal. (*Id.* at 120:20–21). But Dr. Fintel explained that, even so, a POSA would have understood that a combination that lowers blood pressure in non-hypertensive individuals is likely to do so in hypertensive individuals as well. (*Id.* at 120:20–21, 134:10–19). Dr. Fintel called into question Plaintiff's sharp differentiation between heart disease and hypertension by, for example, highlighting drugs that were utilized to treat both conditions. (*Id.* at 52:5–24; *see supra* Section III.B.2.a.i).

Dr. Fintel's testimony is convincing. Notably, Dr. Fintel's testimony is consistent with the conclusion of EP '072, which found that the reported reductions in LVSP and LVEDP are encouraging with respect to hypertension treatment. (JTX 368 at 1, 2).[9] I therefore conclude that a

[9] Thus, I disagree with Plaintiff's argument that Defendants improperly focus on the results that support their position (i.e., the cardiomyopathic hamster data) and ignore the results that don't (i.e., the hypertensive dog data). (D.I. 618 at 5 (citing *In re Wesslau*, 353 F.2d 238, 241 (CCPA 1965)). Although a party cannot "pick and choose from any one reference only as 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," 353 F.2d at 241, I do not think that this is what Defendants have done here. As discussed, Defendants have sufficiently shown that EP '072, considered in its entirety, suggests to a POSA that the disclosed ARB-NEPi combination is encouraging for hypertension.

POSA would view the reductions in LVEDP and LVSP reported in EP '072 Example 1/Trippodo as favorable for hypertension.

Plaintiff contends that certain real-world facts suggest that the EP '072 and Trippodo data were problematic. (D.I. 618 at 6–7). Plaintiff says, "Prior to 2002, BMS abandoned EP '072, and neither BMS nor anyone else clinically developed an ARB/NEP inhibitor combination." (*Id.* at 7). Indeed, BMS withdrew EP '072 in late 2000. (Tr. at 294:20–25 (Dr. Spinale)). It is not clear why, exactly, BMS opted not to pursue the EP '072 application to issuance. Plaintiff does not present evidence on BMS's rationale, and as Defendants note (D.I. 620 at 9), numerous factors other than EP '072 and Trippodo may have impacted its decision. (D.I. 600 at 27 (e.g., another company's ownership of the rights to irbesartan)). It is similarly unclear why no one else picked up BMS's findings and advanced any studies regarding ARB-NEPi combinations for hypertension and heart failure. Thus, I do not afford great weight to Plaintiff's conclusion that the EP '072 and Trippodo data were the cause.

ii. ACEi plus NEPi

Whatever the reason for BMS's decision not to progress with EP '072, BMS turned to an alternative strategy for heart failure and hypertension: omapatrilat, a single molecule that acts as both an ACEi and a NEPi. (Tr. at 295:3–7 (Dr. Spinale); *id.* at 63:4–13 (Dr. Fintel)). Omapatrilat looked promising in early clinical trials; for instance, Cases (JTX-49), which was published in 2000, described vasopeptidase inhibitors (the class to which omapatrilat belongs) as "a promising strategy for the treatment of hypertension and cardiac diseases." (*Id.* at 817 (also stating that omapatrilat "reduces blood pressure to a greater extent than existing agents" and "not only improves [heart failure] symptoms but also reduces the risk of and [sic] hospitalization and death

when compared with ACE inhibitors alone.")). Cases also noted that "the incidence of angioedema with omapatrilat seems to be greater than with ACE inhibitors." (*Id.* at 822).

The parties dispute what happened next. They agree that, in 2000, BMS withdrew its new drug application for omapatrilat due to angioedema issues. (D.I. 619 at 18–19; D.I. 600 at 16–17). The parties disagree on the extent to which a POSA would associate omapatrilat with angioedema. Plaintiff, relying primarily on Dr. Spinale's testimony, suggests that, as of the priority date, angioedema was not perceived to be a significant issue with omapatrilat. (*See, e.g.*, D.I. 619 at 19). I am not convinced. Although Dr. Spinale testified that angioedema was only identified as a problem with omapatrilat after 2002 (Tr. at 312:1–3), BMS's withdrawal suggests otherwise. Furthermore, Dr. Spinale admitted on cross that it was known in the art prior to 2002 that omapatrilat caused angioedema. (*Id.* at 381:10–15).

Nevertheless, I agree with Plaintiff that a POSA in 2002 would consider omapatrilat to be a promising strategy for treating heart failure and hypertension. (*See* D.I. 619 at 18–19 (citing Tr. at 311:12–25 (Dr. Spinale)). Plaintiff says, "While angioedema eventually led to the discontinuation of the development of the dual ACE inhibitor plus NEP inhibitor omapatrilat, that did not occur until after the 2002 priority date." (D.I. 619 at 18). Plaintiff points to evidence suggesting that, shortly before January 2002, clinical development of omapatrilat was, indeed, ongoing. For example, in 2000, Coats (JTX-57) referred to the voluntary withdrawal as "a minor setback" and disclosed that BMS planned to refile with additional data. (*Id.* at 2). And Weber (JTX-197)—which was published a year after BMS's voluntary withdrawal—discussed hypertension and heart failure studies that had been initiated and were ongoing with omapatrilat. (*See id.* at 1528–30). I find Plaintiff's evidence convincing.

3. Comparison of the Prior Art and the Claimed Subject Matter

Defendants offer two theories in asserting the '659 Patent claims are obvious over EP '072, the '996 Patent/Ksander, and the '578 Patent/Diovan® Label. (D.I. 599 at 12–13; D.I. 600 at 21–22). Defendants' first theory starts with the EP '072 ARB-NEPi combination, replaces the NEPi with sacubitril from the '996 patent/Ksander, and replaces the ARB with valsartan from the '578 patent/Diovan® Label. (*Id.*). Defendants' second, alternative theory starts with sacubitril from the '996 patent/Ksander and valsartan from the '578 patent/Diovan® Label and combines them based on EP '072. (D.I. 599 at 13; D.I. 600 at 22–23). Neither theory passes muster.

Central to both theories is the notion that a POSA would have been motivated to pursue ARB-NEPi combinations to treat heart failure and hypertension. (*E.g.*, D.I. 600 at 17). Defendants' primary argument—that a POSA would have understood from EP '072 that the combination of an ARB (irbesartan) and a NEPi (SQ 28,603) achieved synergistic results for the treatment of hypertension and heart failure—is persuasive. *See supra* Section III.B.2.e.i. I am less convinced by Defendants' other arguments. As discussed, I do not think that Cleland would have motivated a POSA to combine a NEPi with an ARB in order to unmask the benefits of the NEPi. *See supra* Section III.B.2.d. And although a POSA would also have understood that ARBs were associated with a reduced risk of angioedema as compared with ACEis, *see supra* Section III.B.2.c, I do not think that this fact helps Defendants. Defendants argue that ARBs' advantage with respect to angioedema would have motivated a POSA to replace the ACEi activity in omapatrilat with ARB activity. (*E.g.*, D.I. 600 at 18). As explained, however, omapatrilat was viewed quite favorably in 2002. *See supra* Section III.B.2.e.ii. I therefore doubt whether a POSA would have sought to modify omapatrilat in 2002.

Ultimately, my findings of fact on the ARB-NEPi combination issue do not affect the outcome of the analysis, as I conclude that—even if a POSA would have been motivated to pursue such a combination—Defendants fail to provide clear and convincing evidence that a POSA would have been motivated to select the ARB valsartan and the NEPi sacubitril specifically.

First, valsartan. Defendants argue, "a POSA would have replaced irbesartan in EP '072 or Trippodo with valsartan." (D.I. 599 at 9). I don't think so. Valsartan was not clearly preferable to irbesartan in 2002. Defendants fail to show that a POSA would view valsartan as a preferred ARB by virtue of its potency, selectivity, or liver enzyme affinity. *See supra* Section III.B.2.c. Furthermore, Plaintiff offers evidence suggesting that irbesartan outperformed valsartan in a clinical context. *See id.* I therefore conclude that that the prior art would not provide motivation for a POSA to replace irbesartan in EP '072 or Trippodo with valsartan.

Second, sacubitril. Defendants argue, "A POSA would have replaced SQ 28,603 in EP '072 or Trippodo with sacubitril." (D.I. 599 at 10). This argument falls short as well. In 2002, the universe of candidate NEPis was large—the prior art disclosed over 100 known NEPis, half of which had demonstrated preclinical activity. (Tr. at 440:10–441:6 (Dr. Klibanov); PTX-1021 (summary exhibit of NEPis disclosed in the prior art); Tr. at 297:21–298:9 (Dr. Spinale); *id.* at 126:23–127:1 (Dr. Fintel)). The two prior art references upon which Defendants rely do not convincingly demonstrate that, among these NEPis, sacubitril was preferred. The '996 patent did not compare sacubitril to any other known NEPis. (Tr. at 297:21–298:9 (Dr. Spinale)). And although Ksander taught that sacubitrilat was more potent than the other NEPis that Ksander synthesized, Ksander evaluated only 31 NEPis in total and did not compare sacubitril or sacubitrilat with SQ 28,603. (*See supra* Section III.B.2.d; JTX-352). Indeed, Defendants do not assert any reason why a POSA would have wanted to replace SQ 28,603 in the first place. Thus, I

conclude that that the prior art would not provide motivation for a POSA to replace SQ 28,603 in EP '072 or Trippodo with sacubitril.

The drug combination cases upon which Defendants rely do not suggest otherwise. Defendants assert that, as "valsartan and sacubitril were known to treat hypertension and heart failure," "it would have been obvious to combine them." (D.I. 599 at 12). Defendants rely upon two cases—*Nalprioprion Pharms., Inc. v. Actavis Lab'ys FL, Inc.*, 934 F.3d 1344 (Fed. Cir. 2019) and *BTG Int'l Ltd. V. Amneal Pharms. LLC*, 923 F.3d 1063 (Fed. Cir. 2019)—for the proposition that "[a] motivation to combine exists where two drugs are disclosed to treat the same condition." (D.I. 599 at 2–3 (citing *Nalpropion*, 934 F.3d at 1353–54)). I agree with Plaintiffs that this characterization oversimplifies the obviousness analysis. 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). As Plaintiffs say: "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." (D.I. 618 at 11 (citing *In re Cyclobenzaprine*, 676 F.3d 1063, 1068–69 (Fed. Cir. 2012))).

The facts of *Nalpropion* and *BTG* are distinguishable from the facts of this case. In *Nalpropion*, the Federal Circuit held that combining naltrexone and bupropion for treating obesity was obvious because (1) the prior art combined naltrexone and bupropion to minimize weight gain; (2) naltrexone caused weight loss in clinical trials; and (3) bupropion caused weight loss in clinical trials. 934 F.3d at 1351–54. In other words, the prior art demonstrated that the exact drugs claimed showed effects relevant to weight loss both individually and in combination. *BTG* presented similar facts. There, the Federal Circuit held that combining prednisone and the CYP17 inhibitor abiraterone to treat prostate cancer was obvious because (1) prior art combined prednisone and the

CYP17 inhibitor ketoconazole to manage prostate cancer; (2) prednisone was already used to treat prostate cancer; and (3) abiraterone was a more selective CYP17 inhibitor than ketoconazole and effectively suppressed testosterone. *BTG*, 923 F.3d 1063, 1074–75. The court's decision rested on its conclusion that abiraterone and prednisone "were both together and individually considered promising prostate cancer treatments at the time." *Id.* at 1074.

Here, no prior art combined valsartan with sacubitril, sacubitril with an ARB, or valsartan with a NEPi. Nor were valsartan and sacubitril both considered promising treatments for cardiac conditions in 2002; NEPis, in particular, had a history of discouraging results for heart failure and hypertension, and sacubitril had never been administered in humans. *See supra* Section III.B.2.d. Most importantly, in my view, is the fact that a large number of hypertension and heart failure drugs and drug classes were known in 2002—including multiple ARBs and a myriad of NEPis—with no clear hierarchy within the ARB and NEPi classes and no available information pointing directly at the claimed valsartan-sacubitril combination. I agree with Plaintiff that, within this wide universe of potential drug combinations, Defendants "make a beeline to valsartan and sacubitril." (D.I. 618 at 13). Defendants stress that "case law does not require that a particular combination must be the preferred, or the most desirable, combination described in the prior art to provide motivation for the current invention." (D.I. 599 at 10 (quoting *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004))). Defendants also emphasize that "there is no need for a POSA to study every compound in a particular class in order to conclude that a particular drug within the class is interesting for further consideration" (D.I. 599 at 9 (citing Tr. at 373:21–24 (Dr. Spinale))). Those statements are true enough. But Defendants must nevertheless provide some reason, suggestion, or motivation in the prior art that would lead a POSA to combine valsartan and sacubitril in particular, *see Forest Lab'ys, LLC v. Sigmapharm Lab'ys, LLC*, 918 F.3d 928, 934 (Fed. Cir.

2019), in view of the invention and of the prior art "as a whole." *In re Langer*, 465 F.2d 896, 899 (CCPA 1972). Defendants have not done so here.

Defendants' alternative, obvious-to-try theory falls short as well. Defendants say, "At minimum, a POSA would have tried valsartan in place of irbesartan" (D.I. 599 at 9), and "sacubitril in place of SQ 28,603." (*Id.* at 10). I disagree. The Supreme Court has explained that "obvious to try" may apply when "there are a finite number of identified, predictable solutions" to a known problem. *KSR*, 550 U.S. at 421. When the path has been identified and "leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense." *Id.* The Federal Circuit has elaborated that the identified path must "present a finite (and small in the context of the art) number of options easily traversed to show obviousness." *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.,* 520 F.3d 1358, 1364 (Fed. Cir. 2008). As illustrated in *In re O'Farrell,* 853 F.2d 894, 903 (Fed. Cir. 1988), it would not be "obvious to try" when "the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful."

The surfeit of potentialities with respect to drug combinations for heart failure and hypertension treatment weighs heavily against Defendants here. Defendants assert in their reply brief that the number of classes of drugs for heart failure and hypertension was finite and easily traversed. (D.I. 620 at 6 (citing Tr. at 52:5–24)). But Defendants do not adduce any evidence to that effect; the testimony they cite, in which Dr. Fintel describes the variety of drug classes available to treat heart failure and hypertension in 2002 (*see* Tr. at 52:5–24), seems to undermine Defendants' point. Defendants disregard those other drugs and drug classes, instead opting to use the invention—an ARB-NEPi combination, or worse, in the case of their second theory, valsartan and sacubitril—as their starting point. "In other words, [Defendants] simply retraced the path of

the inventor with hindsight, discounted the number and complexity of the alternatives, and concluded that the invention … was obvious." *Ortho-McNeil Pharm., Inc.*, 520 F.3d at 1364.

Thus, I find that Defendants have not proven by clear and convincing evidence that claims 1–4 of the '659 Patent are invalid as obvious.

C. Conclusions of Law

Defendants assert that the asserted claims would have been obvious over EP '072 in view of the '578 Patent/Diovan® Label and the '996 Patent. (D.I. 599 at 12). Based on my factual findings, a POSA would not have found it obvious to combine valsartan and sacubitril for the treatment of hypertension and heart failure. I therefore conclude that Defendants have not presenting clear and convincing evidence of obviousness.

The parties also dispute whether secondary considerations would offer support that the asserted claims are not obvious. I do not need to address the secondary considerations. Generally, when secondary considerations are proven, that helps the patentee in an obviousness analysis. When they are unproven, the secondary considerations are neutral, and they do not impact the analysis. Since, even if I were to agree with Defendants that they were entirely unproven, I would still, and do, find that Defendants have not proved obviousness by clear and convincing evidence.

I therefore find that Defendants have not shown by clear and convincing evidence that any of the asserted claims of the '659 Patent are invalid as obvious.

IV. 35 U.S.C. § 112

A. Findings of Fact

1. Background

The active ingredient in Entresto® is LCZ696. (Tr. at 408:11–13 (Dr. Klibanov)). LCZ696 is a non-covalently bound complex ("complex") of valsartan and sacubitril. (*Id.* at 415:8–11 (Dr.

Klibanov)). A complex is a single-component material in which multiple types of molecule are linked together in a non-covalent manner, such as by ionic or hydrogen bonding. (*Id.* at 186:14–19 (Dr. Steed)). Co-crystals and co-salts are types of complexes. (*Id.* at 186:13–24, 190:7–9, 192:10–23 (Dr. Steed)). In contrast to a complex, in a physical mixture of valsartan and sacubitril, those non-covalent associations do not exist. (*Id.* at 403:17–22 (Dr. Klibanov)). LCZ696 was the first complex of valsartan and sacubitril. (*Id.* at 252:23–253:6 (Dr. Steed)). LCZ696 was first synthesized in January 2006. (*Id.* at 205:13–23 (Dr. Steed)).

The priority date of the '659 Patent is January 2002 (D.I. 521-1, Ex. 1 at 11)—that is, four years before the discovery of LCZ696. The parties agree that the '659 Patent does not disclose or suggest complexes of valsartan and sacubitril, and that, as of 2002, a POSA would not have contemplated, foreseen, or envisioned such complexes. (D.I. 599 at 15; D.I. 619 at 33; Tr. at 223:1–17 (Dr. Steed); Tr. at 408:1–7, 457:6–458:24 (Dr. Klibanov)).

A *Markman* hearing involving the '659 Patent was held on June 8, 2021. (*In re Entresto*, D.I. 275). The Court concluded that the claims of the '659 Patent are not limited to physical mixtures of valsartan and sacubitril, and do not exclude combinations of valsartan and sacubitril in the form of a complex. (*In re Entresto*, D.I. 294 at 5–7 (recognizing that "[n]othing in the specification of the '659 [Patent] limits the claims," and "the patentee did not define or disclaim the 'combination' of [valsartan and sacubitril]")). This was Plaintiff's preferred construction. (*Id.*). The parties do not dispute that "the claims at issue are directed to a genus of 'combinations' of sacubitril and valsartan," which includes complexes of sacubitril and valsartan. (D.I. 599 at 29; D.I. 618 at 43).

In its *Markman* opinion, the Court noted Plaintiff's statement that "its two patents 'do not disclose or suggest' a [complexed] embodiment." (D.I. 294 at 7 (citing *In re Entresto*, D.I. 253 at

39)). The Court said, "This [statement] seems to be an admission by [Plaintiff] that, at the very least, there will be a non-frivolous issue of written description and/or lack of enablement as this case proceeds on [Plaintiff's] preferred construction." (*Id.*).

The Court's predictions have borne out. Those written description and lack of enablement issues are before me now. I address them in detail below.

2. Level of Ordinary Skill in the Art

As an initial matter, the parties dispute the identity of a POSA with respect to the '659 Patent. The heart of their disagreement concerns a POSA's familiarity with solid-state chemistry, which is the area of chemistry involved in making complexes. (Tr. at 202:14–19 (Dr. Steed)).

The Federal Circuit has enumerated "a non-exhaustive list of factors that may guide the fact finder in finding the appropriate level of skill in the art. These factors include: (1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field." *Best Medical Int'l, Inc. v. Elekta Inc.*, 46 F.4th 1346, 1353 (Fed. Cir. 2022) (cleaned up). The patent's purpose can also be a relevant factor. *Id.*

Here, a POSA is "a medical doctor or Ph.D. in medicinal chemistry or a related field who is interested in developing new drugs for heart failure and hypertension...." (D.I. 619 at 30–31; Tr. at 47:17–23 (Dr. Fintel); *Id.* at 279:24–280:8 (Dr. Spinale); *Id.* at 399:8–21 (Dr. Klibanov)).[10] Defendants contend that a POSA would have had experience and knowledge in solid-state

[10] The parties appear to agree that this aspect of the POSA definition does not affect the outcome of the invalidity analyses. (*See, e.g.*, D.I. 618 at 35–36 (explaining that the "key aspect" in dispute is to what extent a POSA would have had experience, familiarity, or interest in solid-state chemistry)). Therefore, I adopt Plaintiff's version, noting that adopting Defendants' version instead would not change my conclusions.

chemistry. (*See* D.I. 599 at 5; D.I. 600 at 2–3; D.I. 620 at 11). Defendants present little evidence relating to the factors listed above. Rather, Defendants hinge their argument on the Court's *Markman* opinion. Defendants argue, "Because the scope of the claims has been construed to include crystalline co-crystals, co-salts, and other non-covalently bound complexes, such complexes are part of the relevant art, and a POSA should have experience in, or access to one with experience in, solid-state chemistry, including supramolecular complexes and knowledge of that relevant art." (D.I. 600 at 2; *see also* D.I. 599 at 5 (citing *Best Medical*, 46 F.4th at 1354)). A conclusion to the contrary, Defendants say, would "fly in the face of the Court's claim construction and the positions that [Plaintiff] took to obtain that construction." (D.I. 620 at 11).

Plaintiff disagrees. (D.I. 618 at 35–38; D.I. 619 at 30–31). So do I. First, I do not think that the Court's claim construction decision is dispositive here. As Plaintiff puts it: "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." (*Id.* at 37). I do not think that *Best Medical* helps Defendants. There, the Federal Circuit 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 on the computer." *See Best Medical*, 46 F.4th at 1353–54. The "claimed invention" was therefore relevant to defining the appropriate level of skill in the art. *See id.* at 1354. Here, by contrast, the claims and specification of the '659 Patent do not reference complexes at all. The facts of this case are therefore distinguishable from those of *Best Medical*.

Second, considering the trial record as a whole, I agree with Plaintiff that "[a] POSA would not have had experience, familiarity, or interest in solid-state chemistry … and such art would not be part of the 'pertinent art' of which a POSA is aware." (D.I. 618 at 36). Defendants' only

argument for including solid-state chemistry experience in the POSA definition, and for complexes being a part of the pertinent art, relies on hindsight knowledge—i.e., the knowledge that the asserted claims were later construed to cover complexes of valsartan and sacubitril. Defendants do not point to anything 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.

Plaintiff offers compelling evidence to the contrary. (*See* D.I. 618 at 35–37). The undisputed field of art for the '659 Patent is the treatment of hypertension and heart failure. (Tr. at 125:14–18 (Dr. Fintel); *id.* at 202:25–203:5 (Dr. Steed); *id.* at 411:22–25 (Dr. Klibanov)). The purpose of the '659 Patent is to address a need for an improved treatment for those conditions. *See* '659 Patent at 2:61–64, 2:66–3:5. The specification of the '659 Patent relates to pharmaceutical compositions and methods of using such compositions for treating hypertension or heart failure (Tr. at 45:17–25 (Dr. Fintel)) and is completely silent on complexes of valsartan and sacubitril. (*Id.* at 408:1–3, 452:4–14 (Dr. Klibanov)). Likewise, the claims of the '659 Patent do not disclose or even suggest complexes of valsartan and sacubitril. (Tr. at 259:14–21 (Dr. Steed)).

I therefore conclude that pertinent art does not include solid-state chemistry, and that a POSA would not be familiar with solid-state chemistry.

3. State of the Prior Art

Having adopted Plaintiff's definition of a POSA, I now turn to the issue of that POSA's understanding of complexes in 2002.

As discussed, the parties agree that, as of the 2002 priority date, a POSA 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. (D.I. 619 at 33; D.I. 599 at 29

(admitting "a POSA reviewing the specification as [of] the priority date would not have contemplated, foreseen, or envisioned such complexes")). The parties disagree as to whether a POSA would have been aware of complexes, generally.

Defendants argue, "[C]omplexes generally were known" in 2002. (D.I. 599 at 30). Indeed, generally speaking, complexes were known to exist long before 2002; the earliest known co-crystals were discovered in the late 1700s. (Tr. at 187:19–21 (Dr. Steed)). Whether complexes were known to a POSA in 2002, however, is less clear. Defendants argue in the affirmative. (D.I. 600 at 32). Dr. Steed testified to this effect. (*See, e.g.*, Tr. at 186:20–188:22, 215:23–216:10, 245:11–18). I am not convinced by his testimony. In describing a POSA's awareness of complexes, Dr. Steed cited Ngilirabanga (JTX-240), a review article published in 2021. (*See* Tr. at 186:20–188:22). Dr. Steed explained that Ngilirabanga "summarizes the state of the field … going back all the way through to the time of the filing of the patents in question." (Tr. at 187:14–17).[11] But neither Defendants nor Dr. Steed have explained how, exactly, Ngilirabanga demonstrates that a POSA was aware of complexes in 2002. Dr. Steed cited two additional references published after 2002: Morissette (JTX-252) and Almarsson (JTX-234), both of which were published in 2004. (Tr. at 218:13–222:25). Dr. Steed testified that Morissette and Almarsson taught that, by 2004, co-crystals of drug and drug candidates "represent[ed] a new type of material for pharmaceutical development" (*Id.* at 220:4–221:10 (citing Morissette (JTX-252))) and were "a new and unexplored class." (*Id.* at 222:4–12 (citing Almarsson (JTX-234))). Dr. Steed's testimony does not clearly and convincingly demonstrate that such co-crystals were known to a POSA in 2002.

[11] Defendants have acknowledged that Ngilirabanga is not, and was not admitted as, prior art. (Tr. at 189:10–18).

Defendants rely on a single reference available within the relevant time period: Aakeröy (JTX-254), a 1997 review article published in *Acta Crystallographica* (a journal that publishes results of crystallographic studies). (Tr. at 410:25–411:18 (Dr. Klibanov)). Aakeröy teaches that co-crystal preparation is not routine or easy. (D.I. 600 at 33; JTX-249 at 71–72 (citing JTX-254)). Discussing the application of crystal engineering to the pharmaceutical industry, Aakeröy states, "With several billion dollars at stake (which does tend to make people pay attention), we can expect much more interest in this field over the next few years, not just from the pharmaceutical industry." (JTX-254 at 580). Defendants maintain that Aakeröy shows that complexes were known to a POSA in 2002. (*E.g.*, D.I. 620 at 11–12). Plaintiff counters that a POSA "would not have followed the literature or been aware of solid-state chemistry references such as Aakeröy 1997." (D.I. 618 at 39; D.I. 619 at 33–34). Dr. Klibanov testified to this effect. (Tr. at 410:25–411:18 (opining that a POSA, who is interested in developing new drugs to treat cardiovascular disease, would not follow solid-state chemistry literature)). As I have already found that solid-state chemistry is a different field of art from the '659 Patent and not a subject about which a POSA would be knowledgeable, *see supra* Section IV.A.2, I agree with Dr. Klibanov's testimony.[12]

In short, although the parties agree that the existence of complexes, generally, was known quite a bit before 2002, it is not clear that complexes were known in the art for the purposes of the

[12] As Defendants point out (D.I. 600 at 32), however, Plaintiff appeared to concede at closing argument that complexes were generally known in the art. (*See* Tr. at 540:13–17 ("…Novartis does not dispute that co-crystals generally were known….")). I do not think Plaintiff conceded anything of significance. I think that confusion might arise from the fact that co-crystals were known to some people—just not our POSA. Such confusion underlies another apparent concession that Defendants identify. Defendants say that Dr. Klibanov admitted that a POSA would have been aware of complexes in 2002. (D.I. 600 at 32). Although Dr. Klibanov at one point indicated that, in 2002, a POSA knew that co-crystals existed in the prior art (Tr. at 464:19–465:9), Dr. Klibanov later clarified that he gave that testimony from the perspective of Defendants' definition of a POSA (one with familiarity with solid-state chemistry), not Plaintiff's. (*Id.* at 473:6–12).

'659 Patent. It is even less clear that a POSA in 2002 would have been aware of the use of complexes comprising one or more active pharmaceutical ingredients ("pharmaceutical complexes"). As Plaintiffs note (D.I. 619 at 34), Defendants have not identified any such complex that was known in 2002. Although Dr. Steed testified that pharmaceutical complexes were known in the 2002 timeframe (*see, e.g.*, Tr. at 215:23–216:10, 187:9–18), I agree with Plaintiff (D.I. 619 at 40–41) that Dr. Steed's testimony is largely unsupported. Dr. Steed primarily relied upon Ngilirabanga—again, an article dated nearly two decades after 2002—without explaining how Ngilirabanga was relevant to 2002 knowledge. (*See* Tr. at 187:9–18). Indeed, Dr. Steed's testimony suggests that pharmaceutical co-crystals were a new and little-explored class even in 2013, when Dr. Steed authored and published a paper on the subject. (*See id.* at 256:17–257:5). At the time of the paper, Dr. Steed was not aware of any pharmaceutical co-crystals approved as drug substances. (*Id.* at 256:25–257:5 (Dr. Steed)). The 2013 paper reported that "the possibility of combining two active ingredients in a single co-crystal [was] an interesting one." (*Id.* at 257:6–20 (Dr. Steed)).

4. The Discovery of LCZ696 in 2006

Novartis's scientists first synthesized LCZ696 in January 2006, after conducting over one thousand separate experiments between March 2005 and January 2006. (JTX-355 at 5, 7; JTX-802 at 33:3–7, 33:22–34:5, 40:23–24, 41:2–5, 8–11, 46:14–16, 46:18, 48:18–20, 48:22–49:5, 49:14–18, 49:20 (Dr. Karpinski); Tr. at 205:13–23 (Dr. Steed); *id.* at 408:14–16, 409:2–11 (Dr. Klibanov)). Even in 2005, Novartis's scientists did not know whether it was possible to make a complex of valsartan and sacubitril. (JTX-802 at 114:16–17, 20 (Dr. Karpinski); Tr. at 206:14–207:5, 209:13–17, 242:20–243:5 (Dr. Steed); *id.* at 408:23–409:1 (Dr. Klibanov)). Dr. Karpinski, a Novartis scientist involved in the efforts to create such a complex, described the project as a

"loooong shot" in April 2005 (DTX-643 at NPC-VS-016880042), reported "diminishing hope" for the project's success in August that same year (DTX-645 at NPC-VS-016680066), and, by October, stated that they "ha[d] not yet proven" that such complexes were "feasible." (DTX-646 at NPC-VS-016650514). Another Novartis scientist suggested, also in October 2005, that they "try[] as many and as wild [approaches] as we can" to try to form a complex of valsartan and sacubitril. (DTX-647). According to Dr. Karpinski, they ultimately succeeded in creating LCZ696 using an "Out-of-the-box (Irrational?) Approach." (DTX-359 at NPC-VS-016626522; JTX-802 at 116:22–23, 121:18–23, 122:1 (Dr. Karpinski)).

B. Enablement

1. Legal Standard

The Supreme Court recently reaffirmed that a patent's "specification must enable the full scope of the invention as defined by its claims." *Amgen Inc. v. Sanofi*, 143 S. Ct. 1243, 1254 (2023). For a patent claim to be enabled, the patent specification must "contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same[.]" 35 U.S.C. § 112(a). "The enablement requirement is met where one skilled in the art, having read the specification, could practice the invention without 'undue experimentation.'" *Streck, Inc. v. Rsch. & Diagnostic Sys., Inc.*, 665 F.3d 1269, 1288 (Fed. Cir. 2012) (citation omitted); *see also Amgen*, 143 S. Ct. at 1255 ("[A] specification may call for a reasonable amount of experimentation to make and use a patented invention. What is reasonable in any case will depend on the nature of the invention and the underlying art."). Factors for assessing whether a disclosure would require undue experimentation include:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).

"Enablement is a question of law based on underlying facts." *Wyeth & Cordis Corp. v. Abbott Lab'ys,* 720 F.3d 1380, 1384 (Fed. Cir. 2013). The party challenging validity must prove lack of enablement by clear and convincing evidence. *Cephalon, Inc. v. Watson Pharms., Inc.,* 707 F.3d 1330, 1336 (Fed. Cir. 2013).

The Federal Circuit has consistently held, "Enablement is determined as of the effective filing date of the patent." *Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1339 (Fed. Cir. 2003) (citing *In re Hogan*, 559 F.2d 595, 604 (CCPA 1977)). A patent need not enable later-existing state of the art (i.e., art that comes into existence after the priority date). *Chiron Corp. v. Genentech, Inc.*, 363 F.3d 1247, 1254 (Fed. Cir. 2004); *U.S. Steel Corp. v. Phillips Petroleum Co.*, 865 F.2d 1247, 1249–52 (Fed. Cir. 1989); *Hogan*, 559 F.2d at 605.[13] "Nascent technology, however, must be enabled with a 'specific and useful teaching.'" *Chiron Corp.*, 363 F.3d at 1254 (quoting *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1368 (Fed. Cir. 1997); *see Plant Genetic*, 315 F.3d at 1340 (finding transformed monocot cells needed to be enabled because they were not an unknown concept as of the priority date). Nascent technology is "unpredictable technology in the early stages of development," *Genentech*, 108 F.3d at 1367-68, in which a POSA has "little or no knowledge independent from the patentee's instruction." *Chiron*, 363 F.3d at 1254.

[13] Defendants argue that this portion of *Hogan* is dicta. (*In re Entresto*, D.I. 599 at 23). I disagree. The Federal Circuit has treated this part of *Hogan* as the holding. *See Plant Genetic*, 315 F.3d at 1340 (Fed. Cir. 2003) ("*Hogan* simply held that one could not use a later-existing state of the art to invalidate a patent that was enabled for what it claimed at the time of filing.").

2. Conclusions of Law

The parties dispute whether the specification is required to enable the full scope of the claims. As discussed, this Court has construed the asserted claims to cover valsartan and sacubitril as a physical combination and as a complex. (*See In re Entresto*, D.I. 294 at 5–7). It is not disputed that the specification neither discloses nor suggests a complex of valsartan and sacubitril. (D.I. 599 at 15; D.I. 619 at 33; Tr. at 223:1–17 (Dr. Steed); Tr. at 408:1–7, 457:6–458:24 (Dr. Klibanov)). Accordingly, Defendants argue that the claims are invalid for lack of enablement for not enabling the complex. (*See, e.g.*, D.I. 599 at 16–29). Plaintiff argues that the complex is an after-arising invention that the patent need not enable. (*See* D.I. 618 at 27–43).

The principal cases are *Hogan*, *Plant Genetic*, and *Chiron*. I discuss each case in turn.

First, *Hogan*. There, the CCPA—the predecessor Court to the Federal Circuit—reviewed an appeal for a rejection of a patent application filed in 1953 with claims covering ways to make and use "a solid polymer." 559 F.2d at 606. 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. *Id.* at 604–06. The PTO rejected the claims as non-enabled. *Id.* at 605. The PTO did so because it found that the claims also encompassed a non-crystalline (amorphous) form of the polymer, yet the patent failed to enable that non-crystalline form. *Id.* The non-crystalline form, however, did not exist until 1962—nearly a decade after the patent was filed. *Id.* The CCPA reversed and remanded the case to the PTO. *Id.* at 609. The CCPA held that the PTO had improperly based the enablement rejection on a later-existing state of the art. *Id.* at 604–05. The CCPA explained 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. The Federal Circuit endorsed the CCPA's position in *U.S. Steel*.

See 865 F.2d at 1249–52 (holding that evidence "directed solely to a later state of the art" was insufficient to prove lack of enablement.).

Second, *Plant Genetic*. The patent in *Plant Genetic* taught a plant cell genetically engineered to produce a protein that prevents certain herbicides from blocking the function of glutamine synthetase. 315 F.3d at 1337. Although flowering plants can be broadly categorized as either monocots or dicots, the working examples disclosed in the patent pertained solely to dicots. *Id.* The issue was whether the claims, which the parties agreed covered all plant cells, were required to enable monocot cells. *Id.* at 1338, 1339. The Federal Circuit found that, unlike the amorphous polymer in *Hogan*, "monocots and stably transformed monocot cells were not an unknown concept that came into existence only after" the patent's priority date. *Id.* at 1340; *see also Chiron*, 363 F.3d at 1257 (describing the stably-transformed monocots in *Plant Genetic* as "nascent technology"). Accordingly, the patent was required to enable monocots. *Plant Genetic*, 315 F.3d at 1340–41. The Federal Circuit concluded that the patent had not done so, and its plant cell claims were therefore invalid for lack of enablement. *Id.* at 1344.

Third, *Chiron*. In *Chiron*, the Federal Circuit analyzed whether a patent could claim priority to three earlier patent applications, which were filed in 1984, 1985, and 1986. 363 F.3d at 1249, 1251. The patent claimed monoclonal antibodies that bound to a specified antigen. *Id.* at 1250. The district court broadly construed the claims to cover murine, humanized, and chimeric antibodies. *Id.* at 1252. The 1984 patent application disclosed murine antibodies, but not chimeric antibodies—which was not surprising, as the first publication to disclose chimeric antibody technology did not appear until May 1984, four months after the 1984 patent application was filed. *Id.* at 1251, 1254. The Federal Circuit held, "Because the first publication documenting the successful creation of chimeric antibodies arose after the filing date of the 1984 application, …

this new technology arose after the 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).[14] The Federal Circuit explained that "a patent document cannot enable technology that arises after the date of application. The law does not expect an applicant to disclose knowledge invented or developed after the filing date. Such disclosure would be impossible." *Id.*

The Federal Circuit came to the opposite conclusion with respect to the 1985 and 1986 patent applications. Those applications, like the 1984 application, did not specifically disclose chimeric antibodies; indeed, the later applications "provide[d] no disclosure of either how to make and use chimeric antibodies or working examples of chimeric antibodies" within the scope of patent's claims. *Id.* at 1256. Unlike the 1984 application, however, the 1985 and 1986 applications were filed after the first disclosure of chimeric antibodies. *Id.* The Federal Circuit found that substantial evidence supported the jury's finding that, at the time of these applications, chimeric antibodies were nascent—as opposed to unknown—technology. *Id.* at 1256–57. As chimeric antibodies constituted nascent technology with respect to the 1985 and 1986 applications, they were required to be enabled with "a 'specific and useful teaching.'" *Id.* at 1255 (quoting *Genentech*, 108 F.3d at 1368). The Federal Circuit held that the applications fell short of this requirement. *Id.* at 1256.

Hogan, *Plant Genetic*, and *Chiron* stand for the same proposition: Enablement is judged as of the priority date, and later-existing state of the art may not be properly considered in the enablement analysis. Defendants cite numerous other authorities to support their argument that, "because the law requires that a patent provide an enabling disclosure for the full claim scope of

[14] The Federal Circuit went on to determine the patent could not claim priority to the 1984 application due to inadequate written description. *Id.* at 1255.

the claims, the '659 patent is invalid." (D.I. 599 at 16–20 (citing, *e.g.*, *Trustees of Boston Univ. v. Everlight Elecs. Co.*, 896 F.3d 1357 (Fed. Cir. 2018); *Alza Corp. v. Andrx Pharms., LLC*, 603 F.3d 935 (Fed. Cir. 2010); *Liebel-Flarsheim Co. v. Medrad, Inc.*, 481 F.3d 1371 (Fed. Cir. 2007))). None of these cases contradict *Hogan* and its progeny. As Plaintiff notes, "Each [of these cases] 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*." (D.I. 618 at 33).

The key question is whether the same is true here. Plaintiff argues, "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." (D.I. 618 at 27). Specifically, Plaintiff argues that Defendants have failed to prove that the relevant technology here is nascent technology that existed in the art in 2002, rather than unknown, after-arising technology.[15] (*Id.* at 40–43).

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[15] Plaintiff has not cited any cases holding that a patentee may claim as-yet-undeveloped technology that the patentee did not enable. Such a scenario would present an uneasy discrepancy between the scope of infringement and the scope of enablement. Although the Federal Circuit and the CCPA acknowledged this potential issue in *Hogan* and *Chiron*, both of those cases were decided on other grounds. *See Chiron*, 363 F.3d at 1258; *Hogan*, 559 F.2d at 606–607.

Both opinions contain dicta suggesting that a patentee may indeed claim technology without enabling it. *See Chiron*, 363 F.3d at 1258 (noting that a potential option for construing the claims was to construe the term "broader than the disclosure of the earliest application"); *Hogan*, 559 F.2d at 606–607. In *Plant Genetics*, however, the Federal Circuit explicitly cautioned against reading *Hogan* to "expand the coverage of claims, yet create a new, lower standard of enablement." 315 F.3d at 1341; *see also Chiron*, 363 F.3d at 1262–63 (Bryson, J., concurring).

I am inclined to agree. I think the better approach is to "address cases of new technology by construing claims, where possible, as they would have been understood by one of skill in the art at the time of the invention, and not construing them to reach the as-yet-undeveloped technology that the applicant did not enable." *Chiron*, 363 F.3d at 1263 (Bryson, J., concurring). I did not do the claim construction of the patent in this case, and no one has asked me to revisit it. I have not independently examined it. Thus, I cannot say that I would have construed the claims differently. But I note that had the claims been construed more narrowly, they would have been enabled and have adequate written description.

Before I proceed to that issue, however, I address a threshold question: What, exactly, is the relevant technology? The parties disagree on its proper scope. Defendants characterize the relevant technology broadly; they focus on a POSA's awareness of complexes, generally. (*See, e.g.*, D.I. 599 at 15). Plaintiff, by contrast, characterizes the relevant technology narrowly; it focuses on a POSA's awareness of complexes of valsartan and sacubitril. (*See* D.I. 618 at 40–43).

I think that the correct answer lies somewhere in-between. *Plant Genetic* and *Chiron* are instructive. In both cases, the Federal Circuit characterized the relevant technology as a category somewhat broader than the claimed invention itself. In *Plant Genetic*—where the claims recited plant cells genetically transformed to make the cells invulnerable to a certain herbicide, 315 F.3d at 1337–38—the Federal Circuit characterized the relevant technology as "stably-transformed monocot cells." *See id.* at 1340. In *Chiron*—where the claims recited monoclonal antibodies that bind to a specified antigen, 363 F.3d at 1250—the Federal Circuit characterized the relevant technology as "chimeric antibodies" and "chimeric antibody technology." *See id.* at 1254–55, 1256. Considering these cases, I think that the characterization that Plaintiff urges me to adopt–that is, complexes of valsartan and sacubitril—is too narrow. And I agree with Plaintiff that Defendants' characterization—complexes, generally—is too broad. (*See* D.I. 618 at 40; Tr. at 540:13–541:9). My sense is that an intermediate category, one which bears more directly on a POSA's knowledge of the claimed invention, is appropriate here. One such category is pharmaceutical complexes, which Plaintiff identifies and discusses in its answering brief. (*See* D.I. 618 at 40–41).

For the purposes of this opinion, however, the definition I choose does not affect the outcome of the analysis, as I conclude that, under any of these definitions of the relevant technology, Plaintiff prevails.

First, complexes of valsartan and sacubitril were unknown in the art in 2002. The parties agree on this point. (D.I. 619 at 33; D.I. 599 at 29). The record reinforces it. As Dr. Steed recognized (Tr. at 206:14–207:5, 209:13–17, 242:20–243:5), a team of scientists at Novartis conducted over one thousand experiments to produce a complex of valsartan and sacubitril, and the team did not know whether the project was feasible during the lead-up to the first preparation of LCZ696. *See supra* Section IV.A.4. Thus, complexes of valsartan and sacubitril are later-existing technology that need not be enabled. *See Hogan*, 559 F.2d at 604–07.

Second, I do not think that Defendants offer clear and convincing evidence that pharmaceutical complexes were known in the art in 2002. *See supra* Section IV.A.3. Although Dr. Steed testified that pharmaceutical complexes were nascent technology at that time (*see, e.g.*, Tr. at 187:9–18, 215:23–216:10), Dr. Steed relied on post-2002 references that Defendants do not clearly link to a POSA's knowledge in 2002. The rest of the record does not help Defendants; indeed, Defendants have not identified any pharmaceutical complex known in 2002. This is insufficient. In *Chiron*, "substantial evidence support[ed] a finding" that, when the 1985 and 1986 applications were filed, the relevant technology (chimeric antibodies) was nascent in the field. 363 F.3d at 1256–57 (citing evidence that, for example, only a few laboratories had the capacity and expertise necessary to create genetically engineered antibodies; the techniques facilitating chimeric antibodies' manufacture were not widespread; and pioneers in the field considered chimeric antibodies a new, rather than routine, technology). Similarly, *Plant Genetic* relied upon specific evidence that stably-transformed monocots were nascent technology when the application at issue was filed. *See* 315 F.3d at 1340 (citing evidence that, as of the priority date, monocots existed, stably-transformed monocot cells were highly desirable, and monocot cells were already being stably transformed). Defendants present no such evidence. Accordingly, I think that

pharmaceutical complexes, too, are later-existing technology that need not be enabled. *See Hogan*, 559 F.2d at 604–07.

Finally, I do not think that Defendants offer clear and convincing evidence that complexes, generally, were known in the art in 2002. *See supra* Section IV.A.3. Defendants again rely on post-2002 references without explaining the relevance of those references to 2002. *See id.* And, as explained, I do not think that Defendants' pre-2002 reference (Aakeröy) suggests that complexes were known in the art. *See id.* I therefore agree with Plaintiff that complexes are later-existing technology that need not be enabled. *See Hogan*, 559 F.2d at 604–07.

Accordingly, I find that Defendants have not shown by clear and convincing evidence that any of the asserted claims of the '659 Patent are invalid for lack of enablement.

C. Written Description

1. Legal Standard

The written description requirement contained in 35 U.S.C. § 112 requires that the specification "clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc) (alteration in original). "In other words, the test for sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Id.* "When determining whether a specification contains adequate written description, one must make an 'objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art.'" *Bos. Sci. Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1366 (Fed. Cir. 2011) (quoting *Ariad*, 598 F.3d at 1351).

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*, 598 F.3d at 1350. "[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.* However, "merely drawing a fence around the outer limits of a purported genus is not an adequate substitute for describing a variety of materials constituting the genus and showing that one has invented a genus and not just a species." *Id.*

The written description inquiry is a question of fact. *Id.* at 1351. "A party must prove invalidity for lack of written description by clear and convincing evidence." *Vasudevan Software, Inc. v. MicroStrategy, Inc.*, 782 F.3d 671, 682 (Fed. Cir. 2015).

2. Conclusions of Law

Defendants argue that the '659 Patent is invalid for lack of written description. (D.I. 599 at 29–30; D.I. 620 at 14–15). I agree.

The touchstone of written description is possession as of the priority date. *See Chiron*, 363 F.3d at 1255 (explaining that "'[t]he function of the description requirement is to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter later claimed by him.'") (quoting *In re Wertheim*, 541 F.2d 257, 262 (CCPA 1976)). Defendants contend that, because complexes were unknown as of the 2002 priority date, Plaintiff did not possess such complexes and therefore could not have described them. (D.I. 599 at 30).

Defendants analogize to *Chiron*. (*Id.*). There, the facts that helped the patentee with respect to enablement proved fatal for written description. As discussed, the Federal Circuit held, "Because the first publication documenting the successful creation of chimeric antibodies occurred

after the filing of the 1984 application, … this new technology arose after the filing date and thus was, by definition, outside the bounds of the enablement requirement." 363 F.3d at 1254. But the Federal Circuit went on to explain that, because chimeric antibodies did not exist at the time of the 1984 application, "the Chiron scientists, by definition, could not have possession of, and disclose" the subject matter of such antibodies. *Id.* at 1255. Thus, the Court concluded that, "axiomatically, Chiron cannot satisfy the written description requirement for the new matter appearing in the ['561] patent, namely chimeric antibodies." *Id.*

Such is the case here. It is Plaintiff's position that, in 2002, complexes of valsartan and sacubitril, pharmaceutical complexes, and complexes, generally, were unknown to a POSA. (*See* D.I. 618 at 27, 39–41; D.I. 619 at 33–34). I have found the same. *See supra* Sections IV.A.3, IV.B.2. Thus, I conclude that "the [Novartis] scientists, by definition, could not have possession of, and disclose, the subject matter of [such complexes]" in 2002, and therefore, "axiomatically, [Plaintiff] cannot satisfy the written description requirement" for such complexes. *See Chiron*, 363 F.3d at 1255. The asserted claims are therefore invalid for lack of written description.

Plaintiff's contentions to the contrary (D.I. 618 at 43–44) do not change my mind. Plaintiff argues, "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." (*Id.* at 43 (citing *Ariad*, 598 F.3d at 1350)). Plaintiff points out that physical mixtures of valsartan and sacubitril, and complexes of valsartan and sacubitril, are mere subsets of the claimed genus. (Tr. at 38:9–40:4). According to Plaintiff, written description does not require disclosure of structural features common to only a subset of the claimed genus, and therefore Plaintiff need not have disclosed complexes. (*Id.* at 39:15–40:4).

Plaintiff's trouble is that written description also requires that common structural features be described "with enough precision that a relevant artisan can visualize or recognize the members of the genus." *Regents of the University of Minnesota v. Gilead Sciences, Inc.*, 61 F.4th 1350, 1356 (Fed. Cir. 2023) (citing *Ariad*, 598 F.3d at 1350–52). "A broad outline of a genus's perimeter is insufficient." *Id.* As the Federal Circuit has explained:

> [A]nalogizing the genus to a plot of land, if the disclosed species only abide in a corner of the genus, one has not described the genus sufficiently to show that the inventor invented, or had possession of, the genus. … One describes a plot of land by its furthest coordinates, in effect drawing a perimeter fence around it. That may be akin to the function of patent claims to particularly point out and distinctly circumscribe the outer boundaries of a claimed invention. With the *written description* of a genus, however, merely drawing a fence around a perceived genus is not a description of the genus. One needs to show that one has truly invented the genus, *i.e.*, that one has conceived and described sufficient representative species encompassing the breadth of the genus. Otherwise, one has only a research plan, leaving it to others to explore the unknown contours of the claimed genus.

AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc., 759 F.3d 1285, 1300 (Fed. Cir. 2014). The common features that Plaintiff identifies—sacubitril and valsartan—draw a fence around a genus that includes both complexes and physical mixtures of valsartan and sacubitril. But the '659 Patent specification describes physical mixtures only. The specification did not, and could not, have allowed a POSA to visualize the members of the entire genus sufficient to show possession of complexes, which, to a POSA's knowledge, had not yet been discovered. *See Chiron*, 363 F.3d at 1255.

Accordingly, I find that Defendants have shown by clear and convincing evidence that the asserted claims of the '659 Patent are invalid for lack of written description.

V. INDEFINITENESS

Defendants argue, "[T]he '659 patent's 'about 1:1 ratio' limitation is indefinite because a POSA could not tell whether the claims cover a molar or weight ratio, which result in different claim scopes." (D.I. 599 at 30 n. 4). Defendants argue this in a footnote on the final page of their

opening brief. (*Id.*). I therefore conclude that this argument has been forfeited. *See Higgins v. Bayada Home Health Care Inc.*, 62 F.4th 755, 763 (3d Cir. 2023) ("[T]he District Court was not required to consider [the Plaintiff's argument] because 'arguments raised in passing (such as, in a footnote), but not squarely argued, are considered [forfeited].'") (quoting *John Wyeth & Bro. Ltd. v. CIGNA Int'l Corp.*, 119 F.3d 1070, 1076 n.6 (3d Cir. 1997)).

VI. CONCLUSION

For the foregoing reasons, I find the asserted claims of the '659 Patent invalid for lack of written description. The parties shall submit a final judgment consistent with this memorandum opinion within one week.