**IN THE UNITED STATES DISTRICT COURT**
**FOR THE DISTRICT OF DELAWARE**

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| **SHIRE VIROPHARMA INCORPORATED** | : | |
| | : | **CIVIL ACTION** |
| **Plaintiff,** | : | |
| | : | |
| **v.** | : | |
| | : | **NO. 17-414** |
| **CSL BEHRING LLC and CSL BEHRING GMBH** | : | |
| | : | |
| | : | |
| **Defendants.** | : | |

**Goldberg, J.** **November 18, 2019**

**MEMORANDUM OPINION**

In this patent infringement case, Plaintiff Shire ViroPharma Incorporated ("Plaintiff") alleges that Defendants CSL Behring LLC and CSL Behring GMBH (collectively, "Defendants") have, through the development and marketing of their drug HAEGARDA®, infringed multiple patents owned by Plaintiff. Plaintiff originally alleged infringement of U.S. Patent No. 9,616,111 (the "'111 patent"), the claims of which I have already construed. Plaintiff subsequently alleged infringement of four additional patents—U.S. Patent Nos. 10,080,788 (the "'788 patent"), 10,105,423 (the "'423 patent"), 10,130690 (the "'690 patent"), and 10,201,595 (the "'595" patent)—which share the same specification as the '111 patent and which are collectively known as the "Continuation Patents."

The parties now seek construction of three of the Continuation Patents' disputed terms pursuant to Markman v. Westview Instruments, Inc., 52 F.3d 967, 976 (Fed. Cir. 1995), aff'd, 517

U.S. 370 (1996). The disputed claim terms are construed as indicated in this Memorandum and accompanying Order. [1]

## I. FACTUAL BACKGROUND

### A. Hereditary Angioedema

Hereditary angioedema ("HAE") is a rare genetic disorder causing insufficient natural production of functional or adequate amounts of a protein called C1 esterase inhibitor ("C1-INH"). This protein helps to regulate several complex processes involved in immune system function and fibrinolytic system function. HAE exists in two forms. Type I occurs where the individual produces either no or low C1-INH. Type II is present where the individual has the normal amount of C1-INH, but it does not properly function. (Sec. Am. Compl. ¶ 12.)

Patients suffering from HAE experience symptoms including unpredictable, recurrent attacks of swelling commonly affecting the hands, feet, arms, legs, face, abdomen, tongue, genitals, and larynx. Currently, there are approximately 6,500 people in the United States who suffer from this condition. (Id.)

HAE may be treated by administration of a drug containing a C1 esterase inhibitor in order to restore the levels of C1-INH to levels sufficient to prevent or reduce the frequency or severity of HAE attacks. HAE can be treated either acutely—meaning immediate treatment of an HAE attack in order to slow it down or stop it altogether, or prophylactically—meaning administration of a medication on a regular basis to prevent attacks. (Id. ¶ 13.)

[1] On May 18, 2017, Chief Judge D. Brooks Smith of the United States Court of Appeals for the Third Circuit designated me as a visiting judge for the District of Delaware, pursuant to 28 U.S.C. § 292(b), to handle this and other Delaware cases.

**B. The Patents-in Suit**

1. The ’788 patent

On September 25, 2018, the United States Patent and Trademark Office (“PTO”) issued the ’788 patent, entitled “C1-INH Compositions and Methods for the Prevention and Treatment of Disorders Associated With C1 Esterase Inhibitor Deficiency.” The claims of the ’788 patent are directed generally to

> [A] method for prophylactic treatment of hereditary angioedema (HAE) comprising subcutaneously administering . . . a pharmaceutical composition comprising C1 esterase inhibitor, sodium citrate, and having a pH ranging from 6.5–8.0, wherein the C1 esterase inhibitor has a concentration of about 500 U/mL . . . [The administration of the composition] increases the level of the C1 esterase inhibitor in the blood of the subject to at least about 0.4 U/mL, [and the] C1 esterase inhibitor comprises the amino acid sequence of residues 23 to 500 of SEQ ID NO: 1, [which amino acid sequence is identified in the ’788 patent.]

Plaintiff is the assignee and owner of all rights, title, and interest in the ’788 patent. (Id. ¶¶ 20–22.)

2. The ’423 Patent

On October 23, 2018, the PTO issued the ’423 patent, entitled “C1-INH Compositions and Methods for the Prevention and Treatment of Disorders Associated With C2 Esterase Inhibitor Deficiency.” The claims of the ’423 patent are directed generally to

> [A] pharmaceutical composition comprising C1 esterase inhibitor, sodium citrate, and having a pH ranging from 6.5–8.0, wherein the C1 esterase inhibitor comprises the amino acid sequence of residues 23 to 500 of SEQ ID NO: 1, [which amino acid sequence is identified in the ’423 patent.]

Plaintiff is the assignee and owner of all rights, title, and interest in the ’423 patent. (Id. ¶¶ 23–25.)

3. The ’690 Patent

On November 20, 2018, the PTO issued the ’690 patent, entitled “C1-INH Compositions and Methods for the Prevention and Treatment of Disorders Associated With C1 Esterase Inhibitor Deficiency.” The claims of the ’690 patent are directed generally to

> [A] pharmaceutical composition comprising C1 esterase inhibitor, sodium citrate, and having a pH ranging from 6.5–8.0, wherein the C1 esterase inhibitor has a concentration of about 400–600 U/mL, and wherein the C1 esterase inhibitor comprises the amino acid sequence of residues 23 to 500 of SEQ ID NO: 1, [which amino acid sequence is identified in the ’690 patent.]

Plaintiff is the assignee and owner of all rights, title and interest in the ’690 patent. (Id. ¶¶ 26–28.)

4. The ’595 Patent

On February 12, 2019, the PTO issued the ’595 patent, entitled “C1-INH Compositions and Methods for the Prevention and Treatment of Disorders Associated With C1 Esterase Inhibitor Deficiency.” The claims of the ’595 patent are directed generally to

> [A] method for prophylactic treatment of hereditary angioedema (HAE) comprising subcutaneously administering . . . a pharmaceutical composition comprising C1 esterase inhibitor, sodium citrate, and having a pH ranging from 6.5–8.0, wherein the C1 esterase inhibitor has a concentration of about 400–600 U/mL . . . . [The administration of the composition] increases the level of the C1 esterase inhibitor in the blood of the subject to at least about 0.4 U/mL, [and the] C1 esterase inhibitor comprises the amino acid sequence of residues 23 to 500 of SEQ ID NO: 1, [which amino acid sequence is identified in the ’595 patent.]

Plaintiff is the assignee and owner of all rights, title, and interest in the ’595 patent. (Id. ¶¶ 29–31.)

**C. Defendants’ Alleged Infringement**

On or about July 25, 2017, Defendants began U.S. sales of HAEGARDA®, a prophylactic C1 esterase inhibitor treatment for subcutaneous administration, which received FDA approval on

June 22, 2017. Plaintiff alleges that Defendants' manufacture, importation, use, sale, and/or offer to sell HAEGARDA in the United States directly infringes, induces others to infringe, and/or contributorily infringes, either directly or under the doctrine of equivalents, one or more claims of the Continuation Patents. (Id. ¶¶ 32–100.)

**D. Procedural History**

On April 11, 2017, Plaintiff filed a patent infringement action against Defendants—under Civil Action No. 17-414. In connection with that action, and by way of Memorandum and Order dated January 18, 2019, I construed two terms: (1) the phrase "treating hereditary angioedema" and (2) the phrase "increases the level of C1 esterase inhibitor in the blood of the subject up to about 1 U/mL."

Subsequently, on September 25, 2018, the PTO issued the '788 patent to Plaintiff, which is a continuation of the '111 patent. Plaintiff filed a new complaint in this matter on the same day—under Civil Action No. 18-1476—alleging that Defendants' HAEGARDA product also infringed at least claim 1 of the '788 patent. The PTO then issued two other continuation applications: the '423 patent (October 23, 2018) and the '690 patent (November 20, 2018). Following a status conference, I directed that Plaintiff file an amended complaint in Civil Action No. 18-1476.

Plaintiff filed its First Amended Complaint on January 7, 2019, alleging infringement of at least claim 1 of the '788 patent, the '423 patent, and the '690 patent. The PTO then indicated that a fourth continuation patent—the '595 patent—would issue on February 12, 2019. The parties agreed that Plaintiff would file a second amended complaint to include the '595 patent. As noted above, the Second Amended Complaint sets forth four counts of infringement, one for each of the four Continuation Patents ('788, '423, '690, and '595).

On January 24, 2019, I administratively closed Civil Action No. 18-1476 and consolidated it with the original action under Civil Action No. 17-414.

Currently pending are claim construction issues with respect to the Continuation Patents. There are three terms in dispute.[2]

## II. STANDARD OF REVIEW

The first step in a patent infringement analysis is to define the meaning and scope of the claims of the patent. Markman, 52 F.3d at 976. Claim construction, which serves this purpose, is a matter of law exclusively for the court. Id. at 979. "'[T]here is no magic formula or catechism for conducting claim construction.' Instead, the court is free to attach the appropriate weight to appropriate sources 'in light of the statutes and policies that inform patent law.'" SoftView LLC v. Apple Inc., No. 10-389, 2013 WL 4758195, at *1 (D. Del. Sept. 4, 2013) (quoting Phillips v. AWH Corp., 415 F.3d 1303, 1324 (Fed. Cir. 2005)).

"It is a bedrock principle of patent law that the claims of a patent define the invention to which the patentee is entitled the right to exclude." Phillips, 415 F.3d at 1312 (internal quotation marks omitted). The focus of a court's analysis must therefore begin and remain on the language of the claims, "for it is that language that the patentee chose to use to 'particularly point[ ] out and distinctly claim[ ] the subject matter which the patentee regards as his invention.'" Interactive Gift Express, Inc. v. Compuserve, Inc., 256 F.3d 1323, 1331 (Fed. Cir. 2001) (quoting 35 U.S.C. § 112, ¶ 2). The terms used in the claims bear a "heavy presumption" that they mean what they say and have their ordinary and customary meaning. Texas Digital Sys., Inc. v. Telegenix, Inc., 308 F.3d

[2] At the claim construction hearing, five terms were in dispute. By letter dated November 13, 2019, the parties advised the Court that two of the disputes had been resolved, leaving only three terms left for construction. (ECF No. 236.) Those three terms are the subject of this Memorandum Opinion.

1193, 1202 (Fed. Cir. 2002). That ordinary meaning "is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." Phillips, 415 F.3d at 1313.

Generally, a person of ordinary skill in the art would not understand the ordinary and customary meaning of a claim term in isolation. As such, the ordinary meaning may be derived from a variety of sources including intrinsic evidence, such as the claim language, the written description, drawings, and the prosecution history; as well as extrinsic evidence, such as dictionaries, treatises, or expert testimony. Dow Chem. Co. v. Sumitomo Chem. Co., Ltd., 257 F.3d 1364, 1373 (Fed. Cir. 2001).

The "most significant source" of authority is "the intrinsic evidence of record, i.e., the patent itself, including the claims, the patent specification[3] and, if in evidence, the prosecution history." Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed. Cir. 1996); see also Phillips, 415 F.3d at 1313 (holding that a person of ordinary skill in the art is deemed to read the claim terms in the context of the entire patent, including the specification). The specification "is the single best guide to the meaning of a disputed term" and is usually dispositive as to the meaning of words. Vitronics, 90 F.3d at 1582. Although it is improper to import limitations from the specification into the claims, "one may look to the written description to define a term already in a claim limitation, for a claim must be read in view of the specification of which it is a part." Renishaw PLC v. Marposs Societa' per Azioni, 158 F.3d 1243, 1248 (Fed. Cir. 1998). On occasion, "the specification may reveal a special definition given to a claim term . . . that differs

[3] The specification is "that part of a patent application which precedes the claim and in which the inventor specifies, describes, and discloses the invention in detail." McCarthy's Desk Encyclopedia of Intellectual Property 408 (2d ed. 1995).

from the meaning it would otherwise possess. In such cases, the inventor's lexicography governs." Phillips, 415 F.3d at 1316. The specification may also "reveal an intentional disclaimer, or disavowal, of claim scope by the inventor . . . [, which] is regarded as dispositive." Id. "The construction that stays true to the claim language and most naturally aligns with the patent's description of the invention will be, in the end, the correct construction." Renishaw, 158 F.3d at 1250.

The court "should also consider the patent's prosecution history, if it is in evidence." Markman, 52 F.3d at 980. This consists of "the complete record of proceedings before the Patent Office and includes the prior art cited during examination." Phillips, 415 F.3d at 1317. "Like the specification, the prosecution history provides evidence of how the [Patent and Trademark Office] and the inventor understood the patent." Id. at 1317. Nonetheless, it is the least probative form of intrinsic evidence because it "represents an ongoing negotiation between the PTO and the applicant, rather than the final product of that negotiation." Id.

If ambiguity still exists after considering all the intrinsic evidence, the court may rely on extrinsic evidence, which is "all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises." Markman, 52 F.3d at 980. "[D]ictionaries, and especially technical dictionaries, . . . have been properly recognized as among the many tools that can assist the court in determining the meaning of particular terminology." Phillips, 415 F.3d at 1318. Additionally, expert testimony can provide background on the technology at issue, explain how it works, speak to what a person of ordinary skill in the art would understand, and establish that a particular term has a particular meaning in the pertinent field. Id. Notably, however, extrinsic evidence is "less significant than the intrinsic record in determining 'the legally operative meaning of claim language.'" C.R. Bard, Inc. v. U.S. Surgical Corp., 388

F.3d 858, 862 (Fed. Cir. 2004) (quoting Vanderlande Indus. Nederland BV v. Int'l Trade Comm'n, 366 F.3d 1311, 1318 (Fed. Cir. 2004)).

Ultimately, during claim construction, "[t]he sequence of steps used by the judge in consulting various sources is not important; what matters is for the court to attach the appropriate weight to be assigned to those sources in light of the statutes and policies that inform patent law." Phillips, 415 F.3d at 303.

## III. DISCUSSION

The claim terms of the Continuation Patents in dispute are: (1) "prophylactic treatment of hereditary angioedema," (2) "pharmaceutical composition," and (3) "the administration of the composition increases the level of C1 esterase inhibitor in the blood of the subject to at least about 0.4 U/mL."[4]

### A. "Prophylactic Treatment of Hereditary Angioedema"

The first disputed claim term is the phrase **"prophylactic treatment of hereditary angioedema,"** which appears in claim 1 of both the '788 patent and the '595 patent. Plaintiff offers the following construction:

> [T]reatment administered to HAE patients at regular intervals before an attack, resulting in avoiding future HAE attacks or reducing the frequency and/or severity of future attacks.

Defendants' alternative proposed construction is:

> [T]reatment resulting in a decrease in the probability that the subject will develop HAE or HAE attacks.

The distinctions between the parties' proposals are three-fold. First, Plaintiff seeks to define "prophylactic treatment" as treatment designed to avoid future HAE attacks or reduce the

[4] These terms are used in various claims of the Continuation Patents. My construction of the claim terms applies to all of the Continuation Patents in which they are used.

frequency or severity of future attacks, whereas Defendants want to define "prophylactic treatment" as decreasing the possibility of developing the condition of HAE or the onset of HAE attacks. Second, Plaintiff suggests limiting "prophylactic treatment" to administration of the drug at "regular intervals." Defendants oppose this construction. Third, Plaintiff's proposed definition refers to HAE "patients," whereas Defendants' proposed definition refers to HAE "subjects." I address each of these arguments individually.

1. Whether "Prophylactic Treatment" Includes Avoiding Future HAE Attacks or Reduction in the Frequency or Severity of Future Attacks

As an initial point of reference, I turn to the specification and any relevant definitions. "The specification is the single best guide to the meaning of a disputed term." Pressure Prods. Med. Supplies, Inc. v. Greatbatch Ltd., 599 F.3d 1308, 1314–15 (Fed. Cir. 2010) (quotations omitted). "When a patentee explicitly defines a claim term in the patent specification, the patentee's definition controls." Martek Biosicences Corp. v. Nutrinova, Inc., 579 F.3d 1364, 1380 (Fed. Cir. 2009).

The Continuation Patents at issue contain no express definition of "prophylactic treatment." However, two other definitions found within the '788 and the '595 patents are instructive.

First, both patents provide a definition of the related term "prevent," which references "prophylactic treatment." "Prevent" is defined as:

> *The prophylactic treatment* of a subject who is at risk of developing a condition (e.g., HAE or HAE attack) resulting in a decrease in the probability that the subject will develop the condition.

('788 Patent, col. 6, lines 32–35; '595 Patent, col. 6, lines 33–36 (emphasis added).) Defendants suggest that the term "prevent" is interchangeable with the term "prophylactic treatment." I disagree because the express term used in claim 1 of the patents is "prophylactic treatment of

hereditary angioedema," not "prevention of heredity angioedema." Thus, while the term "prophylactic treatment" is contained within the definition of "prevent," a claim construction of "prophylactic treatment" cannot be limited to the definition of "prevent."

Both the '788 and the '595 patents also define the term "treat," which is part of the term "prophylactic treatment." According to that definition:

> The term "treat" as used herein refers to any type of treatment that imparts a benefit to a patient afflicted with a disorder, including improvement in the condition of the patient (e.g., in one or more of the symptoms), delay in the progression of the condition, etc. In a particular embodiment, the treatment of HAE results in at least a reduction in the severity and/or number of HAE attacks.

('788 patent, col 6, lines 36–43; '595 patent, col. 6, lines 37–43.)

My prior claim construction of the '111 patent defined the term "treating" as "[a]ny type of treatment that imparts a benefit to a patient afflicted with HAE, including improvement in the condition of the patient (e.g., in one or more symptoms), delay in the progression of the condition, etc. In a particular embodiment, the treatment of HAE results in at least a reduction in the severity and/or number of HAE attacks."[5] Shire ViroPharma, Inc. v. CSL Behring, LLC, No. 17-414, 2019 WL 266327, at *5 (D. Del. Jan. 18, 2019). Importantly, I also concluded that "prophylactic treatment" was a subset of "any type of treatment" and involved "at least a reduction in the severity and/or number of HAE attacks." Id. at *5–6.

Reading the definitions of "prevent" and "treat" together, in conjunction with my prior construction of "treating," suggests that proper construction of the term "prophylactic treatment"

[5] "[W]e presume, unless otherwise compelled, that the same claim term in the same patent or related patents carries the same construed meaning." Omega Eng'g, Inc, v. Raytek Corp., 334 F.3d 1314, 1334 (Fed. Cir. 2003); see also AstraZeneca AB v. Andrx Labs, LLC, Nos. 14-8030, 15-1057, 2017 WL 111928, at *10 (D.N.J. Jan. 11, 2017) ("[T]he interpretations of the same or other district courts are generally considered to be highly relevant and persuasive authority.").

lies somewhere in the middle of these terms. On one hand, "prophylactic treatment" is narrower than the definition term "treat" and encompasses the "reduction in the severity and/or number of HAE attacks." On the other hand, "prophylactic treatment" appears to fully subsume the definition of "prevent"—which is "prophylactic treatment" resulting in the "decrease in the probability that the subject will develop the condition [HAE or HAE attacks]"—but the term is not clearly limited to just that definition.

For further guidance, I also look to the dependent claims of the Continuation Patents, which are a second source of intrinsic evidence. "Other claims of the patent in question, both asserted and unasserted, can . . . be valuable sources of enlightenment . . . [b]ecause claim terms are normally used consistently throughout the patent . . . ." Phillips, 415 F.3d at 1314. "Differences among claims can also be a useful guide . . . For example, the presence of a dependent claim that adds a particular limitation gives rise to a presumption that the limitation in question is not present in the independent claim." Id. at 1314–15. This "presumption is especially strong when the limitation in dispute is the only meaningful difference between an independent and dependent claim, and one party is urging that the limitation in the dependent claim should be read into the independent claim." SunRace Roots Enter. Co., Ltd. v. SRAM Corp., 336 F.3d 1298, 1303 (Fed. Cir. 2003). "[A] dependent claim cannot be broader than the claim from which it depends." Alcon Research, LTD v. Apotex Inc., 687 F.3d 1362, 1367 (Fed. Cir. 2012). In other words, "independent claims . . . must be at least as broad as the claims that depend from them." AK Steel Corp v. Sollac & Ugine, 344 F.3d 1234, 1242 (Fed. Cir. 2003).

In the patents-in-suit, dependent claim 20 describes, "[t]he method of claim 1, wherein administration of the composition results in at least a reduction in the severity and/or number of HAE attacks." ('788 patent, col. 14, lines 32–34; '595 patent, col. 14, lines 32–34.) As a

dependent claim cannot be broader from the independent claim from which it depends, it stands to reason that the method of claim 1—which references "prophylactic treatment"—must include treatment that "results in at least a reduction in the severity and/or number of HAE attacks." See Trustees of Columbia Univ. in City of New York v. Symantec Corp., 811 F.3d 1359, 1370 (Fed. Cir. 2016) ("[I]n a situation where dependent claims have no meaningful difference other than an added limitation, the independent claim is not restricted by the added limitation in the dependent claim."); Merck Sharp & Dohme Corp. v. Hospira Inc., 221 F. Supp. 3d 497, 520 (D. Del. 2016) (declining to adopt a construction that would exclude a dependent claim from the scope of the claim from which it depends).

Defendants assert that defining the term "prophylactic treatment" in independent claim 1 to be equivalent to language in independent claim 20 is problematic under the fundamental tenet of claim construction in that "the presence of a dependent claim that adds a particular limitation gives rise to a presumption that the limitation in question is not present in the independent claim." (Defs.' Opening Claim. Constr. Br. 14 (quoting Phillips, 415 F.3d at 1314–15).) Defendants reason that to construe "prophylactic treatment" as used in claim 1 of the '788 and '595 patents to include "a reduction in the number and/or severity of attacks" would render dependent claim 20—which is specifically limited to those results—superfluous.

This concern, however, is properly resolved by a construction that takes into account not only "a reduction in the number and/or severity of future attacks"—as found in dependent claim 20—but also "a decrease in the probability that the subject will develop HAE or future HAE attacks"—a phrase not in claim 20. Such a construction will render claim 1 broader than claim 20, thereby avoiding the presumption against redundancy between independent and dependent claims.

A construction that includes both "a reduction in the number and/or severity of future attacks" and "a decrease in the probability that the subject will develop HAE or future HAE attacks" finds support in a third source of guidance—the prosecution history, which "includes the prior art cited during the examination of the patent." Phillips, 415 F.3d at 1317. Like the specification, the prosecution history may be useful in revealing either a special meaning assigned by the patentee to the term or a disclaimer clarifying what the claims do not cover. Id. Prior art references, particularly when cited in the specification or prosecution history "can often help to demonstrate how a disputed term is used by those skilled in the art." Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1584 (Fed. Cir. 1996). Indeed, "[w]hen prior art that sheds light on the meaning of a term is cited by the patentee, it can have particular value as a guide to the proper construction of the term, because it may indicate not only the meaning of the term to persons skilled in the art, but also that the patentee intended to adopt that meaning." Arthur A. Collins, Inc. v. N. Telecom Ltd., 216 F.3d 1042, 1045 (Fed. Cir. 2000); see also Ross-Hime Designs, Inc. v. United States, 126 Fed. Cl. 299, 325 (Fed. Cl. 2016) (adopting, for purposes of claim construction, the definition used in a prior art reference cited in the specification); Katz v. AT&T Corp., 63 F. Supp. 2d 583, 591 (E.D. Pa. 1999) ("A court also may consider the prior art cited in the prosecution history, which may contain clues as to what the claims do not cover.").

Here, during prosecution of the Continuation Patents, Plaintiff cited multiple prior art references that describe "prophylactic treatment of HAE" to include a reduction in the number and severity of attacks. For example, in a patent application entitled "C1 Inhibitor Produced in the Milk of Transgenic Mammals," the term "prophylactic treatment" is used to describe the use of "androgens or fibrinolytic agents . . . *to reduce the number and severity of attacks*." (Pl.'s Opening Claim Constr. Br., Ex. F, at Shire_0000265 (emphasis added).) In another referenced article,

entitled "A Review of Hereditary Angioedema and Recombinant Human C1-Inhibitor Treatment," prophylactic treatments are described as treatments "that *reduce the occurrence of attacks or prevent the anticipated triggering of an attack*." (Pl.'s Opening Claim Constr. Br., Ex. H, at Shire_0001516 (emphasis added).)

Synthesizing all of this intrinsic evidence and my prior claim construction, I conclude that the term "prophylactic treatment," as used in the Continuation Patents, should incorporate portions of the definitions proposed by both parties. Consistent with the definition of "prevent" in the specification—"prophylactic treatment" should include treatment resulting in a decrease in the probability that the subject with develop HAE or future HAE attacks. And consistent with (a) the definition of "treat" in the specification, (b) the dependent claims, and (c) the prosecution history—"prophylactic treatment" should also include treatment that results in reducing the frequency or severity of future HAE attacks.

2. Whether "Prophylactic Treatment" Requires Administration at "Regular Intervals"

The parties have also asked me to construe whether the term "prophylactic treatment" should include administration at "regular intervals." Plaintiff urges the inclusion of the phrase administration at "regular intervals" into the definition of "prophylactic treatment," whereas Defendants posit that this limitation has no foundation in the intrinsic evidence. For the following reasons, I agree with Defendants on this issue.

As noted above, neither the terms "treat" nor "prevent" discuss the method of administration of the C1 esterase inhibitor. Moreover, nothing in the specification injects a limitation directed towards administration at "regular intervals before an attack." To the contrary, the specification discusses the use of dosing "at appropriate intervals" using permissive language:

> The pharmaceutical preparation comprising the molecules of the instant invention *may be* administered at appropriate intervals, for

> example daily, every other day, every three days, five out of every 7 days, or at least one two or three times a week or more until the pathological symptoms are reduced or alleviated, after which the dosage may be reduced to a maintenance level. The appropriate interval in a particular case would normally depend on the condition of the patient.

('788 patent, col. 5, lines 39–47 (emphasis added); '595 patent, col. 5, lines 39–47 (emphasis added).) The dependent claims discuss various means in which the dosing may occur. For example, dependent claims four through six appear to describe a single administration of the C1 esterase inhibitor, whereas claims seven through nine describe particular dosing intervals. ('788 Patent, col. 13, lines 32–38; '595 patent, col. 13, lines 32–38.)

As Plaintiff has offered no support from either the intrinsic or extrinsic evidence suggesting that "prophylactic treatment" requires dosing "at regular intervals," I decline to include this language in the construction of this term.

3. "Patient" versus "Subject"

The final point of dispute on this claim term is whether "prophylactic treatment" involves administration of the C1-INH to an HAE "patient" or to a "subject."

In support of its use of the term "patient," Plaintiff points to my original construction of "treating HAE" in the '111 patent, which I defined as "[a]ny type of treatment that imparts a benefit *to a patient* afflicted with HAE, including improvement in the condition *of the patient* . . ." Shire, 2019 WL 266327, at *13 (emphasis added). As the phrase "prophylactic treatment" includes the definition of "treating," Plaintiff contends that the claim "prophylactic treatment" in the Continuation Patents must also consistently use the word "patient." Plaintiff further contends that the remainder of the specification repeatedly describes the administration of the claimed "pharmaceutical composition" to a "patient" and that the purpose of the invention is to "restor[e] the levels of active C2 esterase inhibitor in these *patients* to or near normal levels." ('788 and '595

patents, col. 1, lines 38–42; col. 2, lines 4–7, col. 5, lines 27–29; col. 5, lines 32–34 (emphasis added).)

Plaintiff's argument, however, disregards the fundamental tenet that claim construction analysis begins "by considering the language of the claims themselves." Trustees of Columbia Univ. in City of New York v. Symantec Corp., 811 F.3d 1359, 1363 (Fed. Cir. 2016). Here, claim 1 of both the '788 Patent and the '595 Patent defines "[a] method of prophylactic treatment" of HAE by "subcutaneously administering *to a subject in need thereof*" the C1 esterase inhibitor. ('788 patent, col. 13, lines 13–16 (emphasis added); '595 patent, col. 13, lines 12–14 (emphasis added).) In describing the invention, the specification provides that "[i]n accordance with the instant invention, compositions and methods for inhibiting (e.g., reducing or slowing), treating, and/or preventing a disorder associated with C2 esterase inhibitor deficiency *in a subject* are provided." ('788 patent, col. 2, lines 18–21 (emphasis added); '595 patent, col. 2, lines 18–21 (emphasis added).) Plaintiff has not explained the difference between the terms "patient" and "subject" or why the actual claim language must be altered to substitute "patient" for "subject." As such, I decline to change the terminology used in the claim language. [6]

For all of the reasons set forth above, I will construe the term "prophylactic treatment of hereditary angioedema" as ***"treatment resulting in a decrease in the probability that the subject will develop HAE or future HAE attacks, or reducing the number and/or severity of future HAE attacks."***

[6] To the extent Plaintiffs seek to substitute the term "patient" in for the term "subject" in any other disputed claim, I reject such construction for the same reasons as set forth herein.

**B. "Pharmaceutical Composition"**

The next disputed claim term is the phrase **"pharmaceutical composition,"** which appears in claim 1 of all four of the Continuation Patents. Plaintiff seeks to construe this phrase as meaning, "a composition for administration to a patient," while Defendants suggest "a *liquid* composition for administration to a subject." In short, Defendants seek to limit the claimed "composition" to liquid form, while Plaintiff's construction does not specify the form of the "composition." For the following reasons, I will adopt Plaintiff's construction of this term.

In support of their added "liquid" limitation, Defendants contend that I must consider the usage of the disputed claim term in the context of the claim as a whole. Abbott Labs. v. Syntron Bioresearch, Inc., 334 F.3d 1343, 1351 (Fed. Cir. 2003). Defendants urge that the claim language teaches a liquid composition because each of the independent claims of the Continuation Patents requires that the "pharmaceutical composition" have a concentration expressed in U/mL. According to Defendants, concentration refers "to the relative amount of a given substance, here C1 esterase inhibitor, in a unit volume, here 1 milliliter." (Defs.' Opening Claim Constr. Br. 7 (citing Oxford Dictionary of Chemistry (4th ed. 2000)).)[7] Defendants explain that given the inclusion of a particular concentration requirement expressed in Units per milliliter, a person of ordinary skill in the art would understand the claimed pharmaceutical composition to be a liquid.

This analysis finds no support in either the claim language itself, the specification, or the dependent claims.

First, the claim language neither expressly nor implicitly teaches a limitation to a liquid pharmaceutical composition. Rather, the claim describes "a pharmaceutical composition

[7] "Dictionary definitions provide evidence of a claim term's 'ordinary meaning.'" Abbott Labs., 334 F.3d at 1350.

comprising C1 esterase inhibitor, sodium citrate, and having a pH ranging from 6.5–8.0, wherein the C1 esterase inhibitor has a concentration of about 500 U/mL . . .” (’788 patent, claim 1; ’595 patent, claim 1; ’423 patent, claim 1, ’690 patent, claim 1.) Notably absent from this language is any requirement that the “composition” be a liquid. The mere presence of a specified concentration in the claim language does not mandate that the invention be in liquid form at the outset, but merely requires that, prior to administration of the invention to a subject, such a concentration must exist.[8]

Defendants’ construction is also at odds with the specification. Here, the specification explicitly provides that “[t]he pharmaceutical composition of the present invention can be prepared, for example, in liquid form, or can be in dried powder form (e.g., lyophilized for later reconstitution).” (’788 Patent, col. 4, lines 38–41.)[9] In other words, the specification clearly describes both a liquid “pharmaceutical composition” and a solid/powder “pharmaceutical composition.” It goes on to state that “[i]n a particular embodiment, the compositions are formulated in lyophilized form. Where the compositions are provided in lyophilized form, the compositions are reconstituted prior to use . . . by an appropriate buffer” including sterile water. (Id., col. 4, lines 42–46.) Thus, to construe “pharmaceutical composition” as a liquid—as Defendants urge—would render meaningless the specification’s statement that the “pharmaceutical composition” could be a lyophilized powder that is later reconstituted.

Plaintiff’s construction also finds support within the doctrine of “claim differentiation,” which “stems from ‘the common sense notion that different words or phrases used in separate

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[8] Defendants argue that the specification only determines what Plaintiff could have claimed, not what it actually claimed. (Defs.’ Answering Claim Constr. Br. 6.) This argument, however, disregards the fact that the claim language does not clearly indicate the form of the “pharmaceutical composition,” notwithstanding its reference to a concentration of C1-INH measured as U/mL.

[9] Where the specifications of the four Continuation Patents are identical, I will cite to only one of the patents.

claims are presumed to indicate that the claims have different meanings and scope.'" Seachange Int'l, Inc. v. C-COR, Inc., 413 F.3d 1361, 1368 (Fed. Cir. 2005) (quoting Karlin Tech. Inc. v. Surgical Dynamics, Inc., 177 F.3d 968, 971–72 (Fed. Cir. 1999)). The doctrine is at its strongest "where the limitation sought to be read into an independent claim already appears in a dependent claim." Seachange, 413 F.3d at 1368–69 (quotations omitted). "To the extent that the absence of such difference in meaning and scope would make a claim superfluous, the doctrine of claim differentiation states the presumption that the difference between the claims is significant." Tandon Corp. v. U.S. Int'l Trade Comm'n, 831 F.2d 1017, 1023 (Fed. Cir. 1987).

The doctrine of claim differentiation renders the addition of any "liquid" limitation invalid. Claim 16 of the '423 and '690 patents teaches, "[t]he pharmaceutical composition of claim 1, wherein the pharmaceutical composition is prepared in liquid form." ('423 patent, col. 14, lines 22–23; '690 patent, col. 14, lines 14–15.) This dependent claim adds a limitation to those recited in the independent claim. Curtiss-Wright Flow Control Corp. v. Velan, Inc., 438 F.3d 1374, 1380 (Fed. Cir. 2006) (stressing that "a dependent claim must add a limitation to those recited in the independent claim"). To read "pharmaceutical composition" in claim 1 to mean a "liquid composition" would make claim 16 superfluous to claim 1, in contravention of the doctrine of claim differentiation. Stated another way, reading claim 1 without the limitation of "liquid" makes dependent claim 16 appropriately narrower in scope than the independent claim from which it depends.

Dependent claim 17 of the '423 and '690 patents reinforces this interpretation, as it teaches "[t]he pharmaceutical composition of claim 1, wherein the pharmaceutical composition is

reconstituted with water from at least one lyophilized powder."[10] ('423 patent, col. 14, lines 24–26; '690 patent, col. 14, lines 16–18.) As noted above, "a dependent claim cannot be broader than the claim from which it depends." Alcon Research, LTD v. Apotex Inc., 687 F.3d 1362, 1367 (Fed. Cir. 2012). Thus, if claim 1 were limited to a "liquid pharmaceutical composition," dependent claim 17—which describes a "pharmaceutical composition" that starts as a lyophilized powder and is then reconstituted with a liquid—would be excluded from the scope of claim 1.[11]

Defendants also cite the prosecution histories of the Continuation Patents. Defendants contend that, in response to obvious rejections during the prosecution of the '788 and '423 patents, Plaintiff argued that "[t]here is ample evidence in the literature that details well-known impediments with regard to converting intravenous dosing of a medicament to subcutaneous dosing of a medicament." (Defs.' Opening Claim Constr. Br., Exs. 13 and 14.) These "well-known impediments" in the literature referred to issues of "viscosity, solubility, and protein aggregation"—problems associated with liquid compositions. (Id.) Based on these references,

[10] Similarly, claim 2 of the '788 patent teaches, "[t]he method of claim 1, wherein the pharmaceutical composition is reconstituted with water from at least one lyophilized powder comprising at least about 2000 U Cl esterase inhibitor and less than about 5000 U C1 esterase inhibitor." ('788 Patent, col. 13, lines 24–28.)

[11] Defendants contend that if the claimed "pharmaceutical composition" includes lyophilized powder, claim 17 of the '423 and '690 Patents would be rendered nonsensical because claim 17 would read "the [lyophilized powder] is reconstituted with water from at least one lyophilized powder." (Defs.' Answering Claim Constr. Br. 9.) Plaintiff, however, does not seek to have "pharmaceutical composition" defined as "lyophilized powder," but rather as "the composition for administration to a patient." Using that definition, claim 17 would more coherently read, "the [composition for administration to a patient] is reconstituted with water from at least one lyophilized powder."

Defendants also argue that the dependent claims do not describe solid and liquid pharmaceutical compositions, but rather two methods of arriving at the claimed liquid "pharmaceutical compositions." That is, the claimed liquid compositions are either (1) made directly in liquid form, or (2) prepared by reconstituting a lyophilized powder in liquid. Such an interpretation is entirely inconsistent with the specification which, as discussed above, provides that the "composition" itself can be in either liquid or dried powder form.

Defendants argue that "[g]iven [Plaintiff's] reliance on alleged difficulties in formulating liquid pharmaceutical compositions to overcome the [PTO's] obviousness rejections," Plaintiff clearly claimed only liquid compositions and "should not be allowed to expand its claim scope to encompass solid pharmaceutical compositions." (Defs.' Opening Claim Constr. Br. 12.)

Defendants' prosecution disclaimer argument is unavailing. Prosecution disclaimer is not appropriate in instances "where the alleged disavowal of claim scope is ambiguous," or where remarks made by an inventor to overcome a rejection may be viewed "as amenable to multiple reasonable interpretations." Omega Eng'g, Inc. v. Raytek Corp., 334 F.3d 1314, 1324 (Fed. Cir. 2003) (citing N. Telecom Ltd. v. Samsung Elec. Co., 215 F.3d 1281, 1293–95 (Fed. Cir. 2000)). Rather, "for prosecution disclaimer to attach, [Federal Circuit] precedent requires that the alleged disavowing actions or statements made during prosecution be both clear and unmistakable." Id. at 1325–26; Cordis Corp. v. Medtronic Ave, Inc., 511 F.3d 1157, 1177 (Fed. Cir. 2008) (reiterating that "arguments made to distinguish prior art references" will be considered disavowals "only if they constitute clear and unmistakable surrenders of subject matter").

Here, Plaintiff's statements to the PTO during prosecution do not constitute a "clear and unmistakable" limitation of the claimed "pharmaceutical composition" to a liquid form. Rather, Plaintiff simply described for the PTO certain difficulties with subcutaneous products that are present regardless of whether the "pharmaceutical composition" is originally in liquid form, or whether it is originally in lyophilized powder form and then reconstituted into a liquid for purposes of administering it to a subject through a syringe. As such, I do not find any clear prosecution history disclaimer.[12]

[12] The parties also reference extrinsic evidence in support of their proposed constructions. As I find that the meaning of this term is clear from the intrinsic record, I decline to consider this evidence. See Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1578, 1583 (Fed. Cir. 1996) ("In

For all of the reasons set forth above, I will construe "pharmaceutical composition" as ***"a composition for administration to a subject."***

### C. "The Administration of the Composition Increases the Level of the C1 Esterase Inhibitor in the Blood of the Subject to at Least About 0.4 U/mL"

The final claim term in dispute is the language in independent claim 1 of the '788 and '595 patents: **"the administration of the composition increases the level of C1 esterase inhibitor in the blood of the subject to at least about 0.4 U/mL."** Plaintiff's proposed construction adopts this precise language, whereas Defendants seek to construe the term as meaning, "the administration of the composition *raises* the level of active C1 esterase inhibitor in the blood of the subject *from below about 0.4 U/mL* to at least about 0.4 U/mL *or higher* after administration of the composition." The parties' dispute focuses on (1) Defendants' use of the word "raises" instead of "increases," and (2) Defendants' addition of "from below about 0.4 U/mL" and "or higher" to the claim language.

The first portion of the dispute—the use of the word "raises" versus "increases"—is easily resolved because Defendants offer no basis for altering the explicit claim language. Indeed, Defendants expressly concede that "raises" and "increases" are "wholly synonymous with one another, and would be understood by a person having ordinary skill in the art as different means of expressing the goal of the claimed inventions: restoration of active C1-INH blood levels." (Defs.' Answering Claim Constr. Br. 17 n.4.) Given this concession, I will adopt the word "increases," as that is the term used in the actual claim language.

The second part of the dispute—Defendants' addition of a baseline level of active C1 esterase inhibitor—requires a more in-depth analysis.

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those cases where the public record unambiguously describes the scope of the patented invention, reliance on any extrinsic evidence is improper.").

Again, I start with the claim language itself. The Federal Circuit has clarified that "[i]f we need not rely on a limitation to interpret what the patentee meant by a particular term or phrase in a claim, that limitation is 'extraneous' and cannot constrain the claim." Renishaw PLC v. Marposs Societa' per Azioni, 158 F.3d 1243, 1249 (Fed. Cir. 1998). "It is improper for a court to add 'extraneous' limitations to a claim, that is, limitations added 'wholly apart from any need to interpret what the patentee meant by particular words or phrases in the claim.'" Hoganas AB v. Dress Indus., Inc., 9 F.3d 948, 950 (Fed. Cir. 1993) (quoting E.I du Pont de Nemours & Co. v. Phillips Petroleum Co., 849 F.2d 1430, 1433 (Fed. Cir. 1998)). Thus, "when a claim term is expressed in general descriptive words, we will not ordinarily limit the term to a numerical range that may appear in the written description or in other claims . . . Nor may we, in the broader situation, add a narrowing modifier before an otherwise general term that stands unmodified in a claim." Renishaw, 158 F.3d at 1249.

Consistent with these principles, the language of the claim term here requires no modification.[13] The claim provides that the administration of the composition "increases the level of C1 esterase inhibitor in the blood of the subject to at least about 0.4 U/mL." As set forth in my prior claim construction opinion, the term "U/mL" refers to "the mean quantity of C1 inhibitor *activity* present in 1 mL of normal human plasma." Shire, 2019 WL 266327, at *18 (emphasis in original). Simply put, the claim requires that once the composition is administered to a subject,

[13] Defendants urge that Plaintiff has waived any objection to Defendants' construction because Plaintiff has not advanced a construction addressing the ordinary meaning of the term "increases." This argument is meritless. Plaintiff clearly proposed a construction of that claim term in the joint claim construction statement and its briefing on claim construction. Simply because Plaintiff's proposed construction substantially adopts the language of the claim term itself—language that seems to require no further construction—does not mean that Plaintiff has waived its argument.

the subject's level of active C1 esterase inhibitor will be above "at least about" 0.4 U/mL. The claim therefore includes not only subjects whose level of C1-INH is below 0.4 U/mL, but also those subjects whose level is already at "about" 0.4 U/mL and needs to be increased. To add in Defendants' proposed language—that the subject's "level of active C1 esterase inhibitor in the blood"[14] must start "from below about 0.4 U/mL"—improperly injects a limitation not present in the claim.[15]

My construction finds ample support in the specification. The specification is silent on any starting level of C1-INH in the subject and discusses solely what the C1-INH level should be after administration of the composition. When describing the background of the invention, the specification clarifies that "restoring the levels of active C1 esterase inhibitor in these patients to or near normal levels is an effective measure for treating HAE." ('788 patent, col. 1, lines 39–42.)

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[14] Defendants' citation to AztraZeneca AB v. Dr. Reddy's Laboratories, Ltd., No. 05-5553, 2010 WL 11414548, at *13 (D.N.J. May 18, 2010) is inapposite. In that case, the court construed the term "increased average plasma levels (AUC) per dosage unit" to mean "greater blood levels of (-)-omeprazole . . . compared to the typical or usual blood levels for omeprazole." Id. at *13. The court found such a construction necessary because the claim term "increased average plasma levels" provided no point of reference on which to determine what were "increased average plasma levels." Id.

By contrast here, the claim language provides a point of reference regarding what the term "increase" means by noting that the level of active C1 esterase in the blood must "increase" to "at least about 0.4 U/mL" regardless of where the C1-INH level started. Contrary to Defendants' argument, Plaintiff's refusal to accord any additional meaning to the term "increases" does not violate any well-settled canons of claim construction.

[15] Indeed, Defendants seem to concede that claim language is not in need of additional construction. In their reply brief, they argue that, "Shire chose to limit its claims to methods where subjects' deficient C1-INH blood levels are *increased to* or above a specific level after administration of the composition. The plain and ordinary meaning of 'increases' clearly contrasts the post-administration blood level of 'about 0.4 U/mL' to the subjects' C1-INH blood levels prior to administration, which are below 0.4 U/mL." (Defs.' Reply Br. 7–8 (emphasis added).) Given that the claim language is clear, and Plaintiff does not dispute that this is what it means, Defendants' additions are unnecessary.

In other words, the focus is on achievement of a specific level of active C1-INH, not on a starting point. The specification goes on to note that "[i]n a particular embodiment, the C1 esterase inhibitor is administered with a frequency and dosage so as to increase the C1 esterase inhibitor level to at least about 0.3, or more particularly, 0.4 U/mL or more up to about 1 U/mL . . . in the blood of the subject." (Id. col. 5, line 66–col. 6, line 4.) Repeatedly, the specification discusses the desired maintenance of about 0.4 U/mL *or higher* for at least 50% of the time, suggesting that a subject whose C1 esterase level starts at or above about 0.4 U/mL would still be included within the claim. (Id. col. 6, lines 4–24.) Moreover, the specification's reference to increasing a subject's C1 esterase inhibitor level "up to about 1 U/mL" indicates that the invention may be used to increase a subject's levels from some number above 0.4 U/mL to up to 1 U/mL.[16]

Likewise, none of Defendants' citations to the prosecution history support their proposed construction. Defendants reference the Declaration of Dr. Jennifer Schranz, submitted to the PTO, which opined that the invention teaches only the achievement of "an appropriate threshold of functional C1-INH activity for routine prophylaxis" and "[p]redicts" the "concentration of functional C1-INH in adult HAE patients receiving certain subcutaneous injections." Dr. Schranz, however, does not cite any baseline starting level. (Defs.' Opening Claim Constr. Br., Ex. 16, ¶ 9 & Fig. 5.)[17] Defendants also reference the Patent Examiner's Notice of Allowability for the '595

[16] Defendants make cursory reference to dependent claims 11–14 of the '788 and '595 patents, which prescribe "maintenance" of the blood levels achieved in independent claim 1 "at or above 0.4 U/mL" for various time periods. Defendants claim that once the level of C1-INH in the blood is raised "to" 0.4 U/mL, this level is maintained "at" 0.4 U/mL for a specified period. Nothing in this argument supports construction of the term "increase" to require inclusion of an original or base level of C1-INH in the blood of the subject.

[17] Defendants argue that Figure 5 of Dr. Schranz's declaration shows that adult HAE subjects' C1-INH blood levels are below the "threshold level" of 0.4 U/mL prior to administration. (Id. at Fig. 5.) This Figure, however, does not confine the open-ended scope of the claim terms. While Dr. Schranz's study tracked adults with starting C1-INH blood levels of below 0.4 U/mL prior to

patent. That document, however, also supports Plaintiff's construction, noting that "[t]he claims are drawn to a method of prophylactic treatment of hereditary angioedema by administration of a subcutaneous formulation . . . to raise the blood level of the inhibitor to at least about 0.4 U/mL." (Defs.' Opening Claim Constr. Br., Ex. 17, at p. 3.) Again, no baseline level is included.

Finally, none of the prior art references submitted during prosecution—on which Defendants now rely—teach the inclusion of a baseline level. (See, e.g., Defs.' Opening Claim Constr. Br., Ex. 18, at 148 (noting that in the common form of the disease, the reduction in functional activity is due to C1-INH concentrations being only 5–30% of normal, but "in the variant form of the disease, immunochemically detectable concentrations of C1-INH are normal or elevated, but a dysfunctional mutant protein is synthesized . . . . Furthermore, functional inadequacy of C1-INH can be transient without any decrease in the level of C1-INH."); Ex. 19, p. 907 (noting only that "for prevention of attacks, subphysiologic levels of C1-inhibitor (as low as 40% of normal levels) are sufficient").)[18]

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administration, the claim language itself does not clearly impose a limitation requiring that subjects have such a baseline level.

[18] In a final effort to bolster their respective positions, both parties cite to extrinsic evidence. Plaintiff specifically references a statement from their expert Andrew MacGinnitie. Dr. MacGinnitie testified at his deposition that, for certain HAE patients, achievement of 0.4 U/mL would not always result in treatment of an HAE attack. (Pl.'s Opening Claim Constr. Br., Ex. M, Dep. of Andrew MacGinnitie, 117:15–23.)

Defendants quote a dictionary definition of "increase" from Webster's Collegiate Dictionary, noting that the term "increase" is defined as "to make greater." (Defs.' Opening Claim Constr. Br., Ex. 20.) Defendants then posit that, to "make greater" requires that the starting point be less than the end result.

I find no need to resort to this extrinsic evidence to properly construe the term "increases," as its meaning is unambiguous and clear from the intrinsic record. See Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1578, 1583 (Fed. Cir. 1996) ("In those cases where the public record unambiguously describes the scope of the patented invention, reliance on any extrinsic evidence is improper.").

Accordingly, I will adopt Plaintiff's proposed construction and define this term as ***"the administration of the composition increases the level of C1 esterase inhibitor in the blood of the subject to at least about 0.4 U/mL after administration of the composition."***

## IV. CONCLUSION

The claims shall be construed as set forth above and in the Claim Construction Order that follows.