IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

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

Goldberg, J. **January 18, 2019**

MEMORANDUM OPINION

Before me is a patent infringement case wherein Plaintiff Shire ViroPharma Incorporated ("Plaintiff") alleges that Defendants CSL Behring LLC and CSL Behring GMBH (collectively, "Defendant") has infringed Plaintiff's U.S. Patent No. 9,616,111 through the development and marketing of Defendant's drug Haegarda®.[1] The parties currently seek construction of two of the patent's disputed terms pursuant to Markman v. Westview Instruments, Inc., 52 F.3d 967, 976 (Fed. Cir. 1995), aff'd, 517 U.S. 370 (1996) ("Markman"). The disputed claim terms are construed as indicated in this Memorandum and accompanying Order.

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").

[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.

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.

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, only approximately 6,500 people in the United States suffer from this condition.

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.

B. <u>The '111 Patent</u>

On April 11, 2017, the United States Patent and Trademark Office ("PTO") issued U.S. Patent No. 9,616,111 (the "'111 patent"), entitled "C1-INH Compositions and Methods for the Prevention and Treatment of Disorders Associated with C1 Esterase Inhibitor Deficiency." The '111 patent is directed to methods of treating hereditary angioedema ("HAE").

Claim 1 recites:

> A method for **treating hereditary angioedema** (HAE) said method comprising subcutaneously administering to a subject in need thereof a composition comprising a C1 esterase inhibitor, a buffer selected from citrate or phosphate, and having a pH ranging from 6.5–8.0, wherein the C1 esterase inhibitor is administered at a concentration **of at least about 400 U/mL** and a dose of at least about 1000 U and wherein the administration of the composition comprising the C1 esterase inhibitor increases the level of C1

> esterase inhibitor in the blood of the subject to at least about 0.4 U/mL, and wherein the C1 esterase inhibitor comprises an amino acid sequence at least 95% identical to residues 23 of 500 of SEQ ID NO:1.

('111 Patent, col. 13, lines 13–25 (emphasis added).)

The remaining asserted claims depend from claim 1. Several of these dependent claims are also at issue here. Claim 3 recites: "[t]he method of claim 1, wherein the composition is administered daily, every other day, or every three days." (Id., col. 13, lines 29–30.) Claim 4 recites: "[t]he method of claim 1, wherein the composition is administered one, two, or three times a week." (Id., col. 13, lines 31–32.) Claims 7, 8, and 9 state:

> 7. The method of claim 1, wherein the administration of the composition comprising a C1 esterase inhibitor results in HAE prophylactic treatment.
>
> 8. The method of claim 1, wherein the administration of the composition comprising a C1 esterase inhibitor results in treatment of an HAE attack.
>
> 9. The method of claim 1, wherein the administration of the composition results in at least a reduction in the severity and/or number of HAE attacks.

(Id., col. 13, line 38–col. 14, line 18.) Finally, claim 15 teaches "[t]he method of claim 1, wherein the administration of the composition comprising the C1 esterase inhibitor increases the level of C1 esterase inhibitor in the blood of the subject up to about 1 U/mL." (Id. col. 14, lines 30–33.)

C. Procedural Background

According to the Second Amended Complaint, on July 25, 2017, Defendants began U.S. sales of a prophylactic C1 esterase inhibitor treatment for subcutaneous administration. Defendants marketed the new C1 esterase inhibitor product as "HAEGARDA," which received FDA approval on June 22, 2017. Defendants immediately issued a press release announcing the availability of HAEGARDA in the United States. (Sec. Am. Compl. ¶¶ 20–21.) The

HAEGARDA product label instructs, in part, that the drug is a "plasma-derived concentrate of C1 Esterase Inhibitor (Human)" to be used for "routine prophylaxis to prevent Hereditary Angioedema (HAE) attacks in adolescent and adult patients." (Id. ¶ 24.) The label further directs HAEGARDA's self-administration by subcutaneous injection. (Id. ¶¶ 20–21, 24, 25.)

Plaintiff initiated this action on April 11, 2017, the same day that the '111 patent issued. It filed its Second Amended Complaint on August 24, 2017, alleging direct infringement, inducement of infringement, contributory infringement, and willful infringement.

On June 18, 2018, the parties submitted opening claim construction briefs setting forth their positions on two disputed terms in the '111 patent. I held a Markman hearing regarding these terms on September 12, 2018. Having fully reviewed the parties' briefing and evidentiary submissions, I now set forth the legal construction of the disputed claim terms.

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 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[2] 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

[2] 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).

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 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

Two claim terms of the '111 patent are in dispute. Specifically, the parties disagree on the correct construction of (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."[3] I address each claim term below.

A. "Treating Hereditary Angioedema"

The first disputed claim term is the phrase "treating hereditary angioedema," which appears in claim 1 of the '111 patent. ('111 patent, col. 13, line 13.) Plaintiff proposes the following construction:

> [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

[3] These claim terms are used in claim 1 of the '111 patent, as well as in several of the dependent claims. Construction of the claim terms applies to the entirety of the '111 patent.

> results in at least a reduction in the severity and/or number of HAE attacks.

(Pl.'s Opening Claim Constr. Br. 4.) Defendant offers a different proposed construction:

> [I]mparting a benefit to a patient experiencing HAE symptoms, including improvement in one or more of the symptoms associated with HAE or delaying the progression of the severity of HAE symptoms, wherein such treatment does not include inhibiting or preventing HAE symptoms.

(Def.'s Opening Claim Constr. Br. 7.)

The distinction between these two proposals lies in the precise definition of the word "treating." Plaintiff posits that "treating" encompasses both acute and prophylactic care, whereas Defendant urges that "treating" is limited to purely acute care. Considering the various sources identified by the parties and for the following reasons, I will adopt Plaintiff's proposed definition.

1. The Definitions Section

"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); see also 3M Innovative Props. Co. v. Avery Dennison Corp., 350 F.3d 1365, 1374 (Fed. Cir. 2003) ("Because 3M expressly acted as its own lexicographer by providing a definition of embossed in the specification, the definition in the specification controls the meaning of embossed, regardless of any potential conflict with the term's ordinary meaning as reflected in technical dictionaries."); Jack Guttman, Inc. v. Kopykake Enters., Inc., 302 F.3d 1352, 1360 (Fed. Cir. 2002) ("Where . . . the patentee has clearly defined a claim term, that definition '[u]sually . . . is dispositive;' it is the single best guide to the meaning of a disputed term.") (quotations omitted).

Here, the '111 patent specification contains a separate "Definitions" section designed to ascribe precise meanings to certain terms within the claims. Although the specific term "treating" is not defined, the verb form "treat" is among the listed definitions. The definition states:

> 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.

('111 patent, col 6, lines 39–45.) As the definition specifically refers to "any type of treatment" imparting a benefit to a patient with HAE and explicitly states that "treatment" includes "at least a reduction in the severity and/or number of HAE attacks," it seemingly includes both acute and prophylactic treatment.

In an effort to rebut this broad language, Defendant remarks that the "Definitions" section separately defines the word "prevent" to mean:

> [T]he 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.

('111 patent, col 6, lines 35–38.) It posits that "[t]he Federal Circuit has consistently . . . [held] that when two terms are defined differently in the specification, one term cannot be construed to encompass the definition of the second term." (Def.'s Answering Cl. Constr. Br. 4 (citing Speedtrack, Inc. v. Endeca Techs., Inc., 524 F. App'x 651, 656 (Fed. Cir. 2013); Trintec Indust., Inc. v. Top-U.S.A. Corp., 295 F.3d 1292, 1296–97 (Fed. Cir. 2002).) Defendant goes on to argue that because these distinct definitions of "treat" and "prevent" do not overlap, they necessarily create a distinction between acute treatment and prophylactic therapy, the latter of which is not included in claim 1.

Defendant's argument is not supported by the specification as a whole. As a general notion, there is a presumption that different terms in a claim have different meanings. Chicago Bd. Options Exchange, Inc. v. Int'l Secs. Exchange, LLC, 677 F.3d 1361, 1369 (Fed. Cir. 2012); accord Primos, Inc. v. Hunter's Specialities, Inc., 451 F.3d 841, 848 (Fed. Cir. 20016). "However, simply noting the difference in the use of claim language does not end the matter. Different terms or phrases in separate claims may be construed to cover the same subject matter where the written description and prosecution history indicate that such a reading of the terms or phrases is proper." Nystrom v. TREX Co., 424 F.3d 1136, 1143 (Fed. Cir. 2005); see also Edwards Lifesciences LLC v. Cook Inc., 582 F.3d 1322, 1330 (Fed. Cir. 2009) (holding that the terms "graft," "graft structure," "bifurcated base structure," and "bifurcated base graft structure" have the same meaning where they were "used interchangeably in the specification and the claims[]"); Hyperphrase Techs., LLC v. Google, Inc., 260 F App'x 274, 278 (Fed. Cir. 2007) (noting that the terms "data reference," "record reference," "specifying reference," and "reference" were interchangeable); St. Clair Intellectual Prop Consultants, Inc. v. Acer, Inc., Nos. 09-354, 09-705, 10-282, 2012 WL 3536454, at *9 (D. Del. Aug. 7, 2012) (finding terms "mode" and "state" could be used interchangeably).

Here, the express language used in the Definitions section overcomes any presumption that "treat" and "prevent" have mutually exclusive meanings. The definition of "treat" is "any form of treatment that imparts a benefit to a patient afflicted with a disorder," such as HAE.[4] This includes prophylactic treatment. Thereafter, "prevent" is defined as "the prophylactic treatment of a subject who is at risk of developing a condition," such as HAE or an HAE attack. Contrary to Defendant's

[4] Defendant interprets "a patient afflicted with a disorder" as a patient with HAE symptoms. However, nothing in the definition suggests that "a disorder" refers to HAE symptoms as opposed to the condition of HAE itself.

argument, "prophylactic treatment" of a person who is at risk of having an HAE attack is a subset of "any type of treatment" for a person with HAE. In other words, the definitions are not mutually exclusive, but rather appear to overlap in order to further refine the broader term of "treat." Had Plaintiff intended to limit the term "treating" to simply acute care, it would not have used the terminology "any treatment."

My interpretation finds additional support in the second sentence of the definition of the term "treat." This language provides that "[i]n a particular embodiment, the treatment of HAE results in at least a reduction in the severity and/or number of HAE attacks." A person of ordinary skill in the art would recognize that this type of "treatment" of HAE refers to prevention of HAE symptoms or attacks. Defendant attempts to dismiss this sentence, arguing that (a) it is a separate sentence and not part of the definition, (b) it merely reflects a "particular embodiment," and (c) it is not needed by a skilled artisan to interpret the term "treat." (Def.'s Cl. Constr. Reply Br. 3–4.) Such an argument, however, effectively reads the sentence out of the specification and renders it superfluous without any countervailing explanation as to why it was included in the definition. See Frans Nooren Afidchtingssystemen B.V. v. Stopaq Amcorr Inc., 744 F.3d 715 (Fed. Cir. 2014) ("It is the usual (though not invariable) rule that, in patent claims as elsewhere, the construction of a clause as a whole requires construction of the parts, with meaning to be given to each part so as to avoid rendering any part superfluous."). Giving meaning to the entirety of the definition before me, I find that it supports Plaintiff's proposed construction.

2. The Remainder of the Specification

Patent claims must also "be read in view of the specification, of which they are a part." Markman, 52 F.3d at 979 (citing Autogiro Co. of Am. v. United States, 384 F.2d 391, 397 (1967)); see also SRI Int'l v. Matsushita Elec. Corp. of Am., 775 F.2d 1107, 1121 (Fed. Cir. 1985). The

specification is "highly relevant to the claim construction analysis" because it contains a written description of the invention that must be clear and complete enough to enable those of ordinary skill in the art to make and use it. Vitronics, 90 F.3d at 1582. "[W]here the ordinary and accustomed meaning of the words used in the claims lack sufficient clarity to permit the scope of the claim to be ascertained from the words alone" the specification can provide clarity. Teleflex. Inc. v. Ficosa N. Am. Corp., 299 F.3d 1313, 1325 (Fed. Cir. 2002). Indeed, "the interpretation to be given a term can only be determined and confirmed with a full understanding of what the inventors actually invented and intended to envelop with the claim." Renishaw, 158 F.3d at1250.

Defendant asserts that the specification repeatedly addresses "treating," "inhibiting" and "preventing" HAE as distinct routes of therapy. As such, Defendant argues that the patent specification repeatedly emphasizes that the compositions and methods of the '111 patent may be directed to either treatment or prevention, thus acknowledging the difference between these two terms. Consequently, Defendant presses that claim 1 limits itself to only one of those embodiments—treating. Based on such a limitation, Defendant asserts that "treating hereditary angioedema" cannot be construed to encompass prophylactic management of HAE attacks. I disagree.

I find that the specification language supports a construction of "treating" that encompasses prophylactic treatment. The specification repeatedly states that "the instant invention provides compositions and methods for the treatment and/or prevention of disorders associated with the C1 esterase inhibitor deficiency." ('111 patent, col. 1 lines 18–22; see also col. 3, lines 44-47 ("As stated hereinabove, the instant invention encompasses methods of treating, inhibiting, and or preventing any condition or disease associated with an absolute or relative deficiency of functional C1 esterase inhibitor."). The specification then discusses a particular embodiment of the invention

wherein the C1 esterase inhibitor is administered on a regular basis in order to maintain the appropriate amounts in the blood, which specifically describes a method of prophylactic, as opposed to acute care. (Id. col. 6, lines 18–25.) Additionally, when describing dosage methods, the specification states that "[t]he high initial do[se] of the C1 esterase inhibitor is optional in the methods of the instantly claimed invention (e.g., may be optional with prophylactic methods)." (Id. col. 5, lines 65–67.) After these various descriptions, the specification—in an apparent effort to encompass these various methods into one term—explicitly defines "treating" to include all forms of treatment of a patient afflicted with HAE, thereby signaling that all of the previously-mentioned methods of care (treating and/or preventing) are encompassed in the term "treat." See Katz v. AT&T Corp., 63 F. Supp. 2d 583, 591 (E.D. Pa. 1999) ("[I]f a term is used in a variety of ways by the patentee in the specification, this may be indicative of the breadth of the term, rather than a limited definition."). Claim 1 then uses the verb "treating" in order to claim "[a] method of treating hereditary angioedema." As the specification describes the patent as an invention designed for both acute and prophylactic treatment, the term "treating," as used in claim 1, would most naturally be read as encompassing both uses.

Reading claim 1 in the context of the entire specification, I conclude that a person of ordinary skill in the art would read the term "treating" in claim 1 to include both acute and prophylactic care.

3. The Dependent Claims

"Other claims of the patent in question, both asserted and unasserted, can also 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). Notably, "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).

Here, dependent claim 7 describes, "the method of claim 1, wherein the administration of the composition comprising a C1 esterase inhibitor results in HAE prophylactic treatment." ('111 patent, col. 13, lines 38–40 (emphasis added).) By its plain language, claim 7 teaches the administration of the C1 esterase inhibitor for prophylactic use. Because a dependent claim cannot be broader than the claim from which it depends, it follows that claim 1 must, at minimum, include both acute and prophylactic treatment. An alternative construction would improperly exclude dependent claim 7 from the scope of independent claim 1 from which it depends. See 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).[5]

Dependent claim 9 bolsters this interpretation. Claim 9 recites: "[t]he method of claim 1, wherein the administration of the composition results in at least a reduction in the severity and/or

[5] Defendant's only response is that claim 7 is an improper dependent claim because it attempts to eliminate a limitation within claim 1. Defendant provides no support for this argument.

number of HAE attacks." (Id., col. 14 lines 15–17 (emphasis added).) While this claim does not use the specific term "prophylactic," it teaches a method of use in part for the purpose of reducing the number of HAE attacks, thereby suggesting prophylactic not acute care. [6]

Finally, under the doctrine of claim differentiation, the inclusion of claim 8 indicates that claim 1 must recite both acute and prophylactic care. (Id., col. 14, lines 12–14.) "The doctrine of claim differentiation stems from 'the common sense notation that different words or phrases used in separate 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 (quotation omitted). "To the extent that the absence of such difference in meaning and scope would make a claim superfluous, the doctrine of

[6] Plaintiff also argues that claims 3 and 4 suggest that prophylactic treatment is part of independent claim 1. Claim 3 recites "[t]he method of claim 1, wherein the composition is administered daily, every other day, or every three days," ('111 patent, col. 13, lines 29–30), while claim 4 recites "[t]he method of claim 1, wherein the composition is administered one, two, or three times a week." (Id., col 13, lines 31–32.) According to Plaintiff, such methods teach regular maintenance doses, as opposed to doses taken on demand when symptoms are present. As explained by Plaintiff's expert Andrew MacGinnitie, "HAE attacks are unpredictable, so acute treatment of HAE is provided to patients at irregular intervals upon the occurrence of an attack . . . . Prophylactic treatment . . . of HAE is treatment administered to HAE patients at regular intervals before an attack, with the goal of avoiding future HAE attacks or reducing the frequency and/or severity of future attacks." (MacGinnitie Decl. ¶¶ 23–24.)

Closer scrutiny of the specification, however, suggests that claims 3 and 4 may actually refer to dosing intervals for treatment of HAE symptoms that a patient is already experiencing. The specification explains that the C1 esterase inhibitor "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." ('111 patent, col. 5, lines 41–47 (emphasis added).) Given this language, claims 3 and 4 could be discussing either acute or prophylactic treatment and, thus, do not support either party's construction.

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).

Claim 8 of the '111 patent recites: "[t]he method of claim 1, wherein the administration of the composition comprising a C1 esterase inhibitor results in treatment of an HAE attack." ('111 patent, col 14, lines 13–15 (emphasis added). To construe "treatment," as used in claim 1, to mean only acute treatment would mean that dependent claim 8, which is specifically limited to acute treatment, would be entirely repetitive of independent claim 1. As the limitation Defendant seeks to read into claim 1 already appears in dependent claim 8, the doctrine of claim differentiation presumes that no such limitation exists in claim 1.[7]

In sum, the dependent claims indicate that the word "treating," as used in claim 1, encompasses both acute and prophylactic care.

4. Prosecution History

The last piece of intrinsic evidence to which the parties refer is the prosecution history of the '111 patent. The patent's prosecution history consists of "the complete record of proceedings before the [Patent and Trademark Office (PTO)] and includes the prior art cited during the examination of the patent." Phillips, 415 F.3d at 1317. Like the specification, the prosecution

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[7] Defendant argues that using its construction of "treating," claim 1 remains broader than claim 8. It reasons that claim 1 is not limited to only treatment of an HAE attack, but also encompasses, for example, improvement in the symptoms associated with HAE itself and delaying the progression of an HAE attack. Claim 8, on the other hand, limits the scope of claim 1 to only a method that results in improving the symptoms associated with an HAE attack itself and not, for example, delaying the progression of an HAE attack.

The distinction identified by Defendant, however, is purely semantical. As discussed above, "treatment"—as used in both claim 1 and claim 8—is defined, in part, as "any 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." The only actual symptoms of HAE are HAE attacks. (MacGinnitie Decl. ¶ 20.) Thus, under Defendant's construction of "treatment," both claim 1 and claim 8 are directed to a delay in or improvement of HAE symptoms after an attack has occurred.

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. The prosecution history may "demonstrat[e] how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution." Id. Thus, examination of a patent's prosecution history and the application of prosecution disclaimer is a helpful tool during claim construction as it "ensures that claims are not construed one way in order to obtain their allowance and in a different way against accused infringers." Chimie v. PPG Indus., Inc., 402 F.3d 1371, 1384 (Fed. Cir. 2005).

The Federal Circuit, however, has warned that a court's reliance on prosecution history must be tempered with the recognition that a "prosecution history represents an ongoing negotiation between the PTO and the applicant, rather than the final product of that negotiation." Phillips, 415 F.3d at 1317. As such, a prosecution history "often lacks the clarity of the specification and thus is less useful for claim construction purposes." Id. 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").

Defendant argues that the prosecution history of the '111 patent confirms that claim 1 does not encompass "inhibiting" or "preventing" HAE symptoms because Plaintiff's original independent claim deleted those terms during the prosecution of the case before the PTO. Specifically, claim 1 of the '111 patent was originally filed as claim 16, and stated:

> 16. (New) A method for treating, inhibiting, or preventing a disorder associated with a deficiency in C1 esterase inhibitor in a subject in need thereof, said method comprising subcutaneously administering to the subject a first composition comprising at least one C1 esterase inhibitor.

(Def.'s Opening Cl. Constr. Br., Ex. 11 at claim 16.)

The Patent Examiner rejected claim 16 as obvious over Jiang, et al., Subcutaneous Infusion of Human C1 Inhibitor in Swine, 136 Clin. Immunol. 323 (2010) ("Jiang"). (Id., Ex. 12.) The Examiner noted that "[t]he Jiang art teaches that Cinryze is approved by the FDA for intravenous administration for prophylactic use in patients with HAE. It is also taught that HAE patients can have a prodrome period of 1–2 hours, during which administration of C1 inhibitor can be given to treat acute attacks of HAE." (Id., Ex. 13, pp. 3–4.) The Examiner went on to state that "[t]he difference between Jiang and the claimed invention is that Jiang does not teach treatment of patients in need thereof in a specific embodiment, but is fairly suggestive of the claimed method." (Id. at 4.)

In response to this rejection, Plaintiff amended claim 16 as follows:

> 16. (Previously Presented) A method for treating~~, inhibiting, or preventing~~ hereditary angioedema (HAE), said method comprising subcutaneously administering to a subject in need thereof a composition comprising a C1 esterase inhibitor, a buffer selected from citrate or phosphate, and having a pH ranging from 6.5-8.0, wherein the C1 esterase inhibitor is administered at a concentration of at least about 400 U/mL and a dose of at least about 1000 U, and wherein the administration of the composition comprising the C1 esterase inhibitor increases the level of C1 esterase inhibitor in the blood of the subject to at least about 0.4 U/mL.

(Id., Ex. 14, p.2.) Plaintiff subsequently re-amended claim 16, upon the suggestion of the Examiner, to include at the end: ". . . and wherein the C1 esterase inhibitor comprises an amino acid sequence at least 95% identical to residues 23 to 500 of SEQ ID NO:1." (Id., Ex. 15, p. 3.) Claim 16 then issued as claim 1.

Defendant now contends that "inhibiting" and "preventing" HAE were therapeutic options intentionally removed from claim 1, and by removing "preventing" from pending claim 16, Plaintiff specifically removed prophylactic therapy from the scope of the claim. Defendant goes on to assert that Plaintiff's deletion of "inhibiting" and "preventing"—done in an effort to overcome the prior art of Jiang, which taught the prophylactic prevention of HAE attacks—comprises a clear and unmistakable disclaimer of claim scope. In turn, according to Defendant, Plaintiff narrowed the meaning of the claim to teach only acute treatment of HAE attacks.

A closer review of the prosecution history undermines any notion that Plaintiff's elimination of the terms "inhibiting" and "preventing" constituted the requisite unambiguous disavowal of a claim scope that includes prophylactic treatment. Defendant is correct that, on July 12, 2016, the patent Examiner rejected Plaintiff's then-pending claims as obvious over Jiang. The study in Jiang:

> sought to assess whether reasonable levels of functional human C1 inhibitor could be achieved in swine plasma following SQ [subcutaneous] administration, to compare plasma levels of human C1 inhibitor administered SQ vs IV (intravenously), to assess the time to peak levels and duration of maintenance, and to assess the safety of subcutaneously administered human C1 inhibitor in an acute-use study.

(Def.'s Opening Cl. Constr. Br., Ex. 12, at 0001477.) In its conclusions, Jiang provided:

> Availability of a SQ route of administration for human C1 inhibitor would represent a significant new treatment option for patients with HAE. The current study suggests that SQ infusion is a viable

> possibility for administering human C1 inhibitor to patients with HAE on prophylactic therapy with no need for intravenous administration. This approach warrants further study. Since some patients have predictable prodromes of 1–2 h and it is known that, the earlier treatment is started, the more likely it is that patients will respond to therapy rapidly, this may provide a new approach to acute treatment in selected patients.

(Id. at 0001481 (emphasis added).)

The Patent Examiner recognized that the Jiang art taught both prophylactic and acute use in patients with HAE through intravenous administration, and concluded that "subcutaneous administration is a viable option for patients with HAE." (Def.'s Opening Cl. Constr. Br., Ex. 13, at 0000904–05, 0000907.) The obviousness rejection was based on the Examiner's finding that "[i]t would be obvious to one of ordinary skill in the art at the time of invention that the subcutaneous of Cinryze to pigs as taught in Jiang could also be applied to human patients suffering from HAE, given that Jiang teaches that Cinryze is already administered to said patients to treat HAE, albeit intravenously." (Id. at 0000906.) Nothing in the Examiner's rejection was directed to the scope of the phrase "treating, inhibiting, or preventing." Indeed, the Examiner rejected dependent claims that were directed to both acute and prophylactic treatment, suggesting that the rejection in light of Jiang had nothing to do with whether the scope of the claim involved both acute and prophylactic treatment. (Id. at 0000907.)

In response to the rejection, Plaintiff filed a Response to Final Offense Action which amended then-claim 16 as described above. In amending its claims, Plaintiff explicitly remarked that "Claims 16 and 53 are amended without disclaimer." (Defs.' Opening Cl. Constr. Br., Ex. 14, at Shire_0000851 (emphasis added).) Additionally, Plaintiff re-proposed dependent claims 34 and 46, which were expressly directed to the method of claim 16 wherein the administration of the C1 esterase inhibitor resulted in HAE prophylactic treatment. (Id. at Shire_0000849–50.) Plaintiff's

accompanying written remarks addressed how the reformulated claims avoided the obviousness problems with Jiang, focusing on the subcutaneous administration of C1-INH at high dosages:

> As acknowledged by Examiner, Jiang teaches subcutaneous administration of CINRYZE, a low concentration (e.g. 100 U/mL) human C1-INH. While Jiang appears to suggest that subcutaneous administration is a viable treatment option, it does not teach or suggest in any way that C1-INH should be injected subcutaneously at a high concentration of at least about 400 U/mL [as taught by the proposed '111 patent].

(Id. at Shire_0000852 (emphasis added).) At no point was there any dialogue between Plaintiff and the Examiner regarding use of the drug for acute versus prophylactic purposes. Nor was the definition of "treat" in the specification ever amended.

Following these amendments, the Examiner notified Plaintiff that he would accept the independent claims, as well as the dependent claims directed to acute and prophylactic treatment. The Examiner provided the following "statement of reasons for allowance:"

> The closest prior art (Jiang as previously cited) teaches administration of C1-INH subcutaneously at a dose of 100 U/mL. However, the instant claims require a dose of at least 400 U/mL, which is not provided by the prior art. The declaration and evidence as submitted by the Applicants as of 11 November 2016 has been found sufficient by the Examiner to establish secondary considerations in the form of long felt need and failure of others (MPEP 716.04) to rebut the prima facie case of obviousness. As no obviousness rejection can be made in light of the secondary consideration and nothing in the prior art suggests the instant dosages as instantly claims for subcutaneous administration, the claims are found to be novel and unobvious.

(Def.'s Opening Cl. Constr. Br., Ex. 15, Shire_0000233.) Nothing in the Examiner's statement of reasons suggested that Plaintiff's deletion of "inhibiting, or preventing" had anything to do with his approval. (Id.)

Although Plaintiff undeniably deleted the terms "inhibiting" and "preventing" from claim 16 (now claim 1), Plaintiff plausibly explains that because the definitions of "treat" and "prevent"

in the patent specification overlapped, it was redundant to include both "treating" and "preventing" in the independent claim. Thus, the amendment allowed the claim language to be simplified. Such an explanation remains entirely consistent with the prosecution history and the obviousness issues identified by the Examiner, which, at no point, expressed any concern with having the scope of the patent include both acute and prophylactic use. In light of the language of the claims and the specification and absent a "clear and unmistakable surrender" of prophylactic use, the prosecution history does not support Defendant's interpretation.[8]

In a last-ditch effort to urge that the prosecution history requires that I ascribe a more limited meaning to the term "treating," Defendant cites to Laryngeal Mask Co. Ltd. v. Ambu, 618 F.3d 1367 (Fed. Cir. 2010). In that matter, the patent claimed a laryngeal-mask airway device comprising, inter alia, a backplate defining passage to deliver air and other gases into a patient's lungs. Id. at 1368. The parties disputed the construction of the term "backplate" as used in the patent. Id. at 1370–71. Although the original claims of the patent disclosed a "tube joint" limitation attaching the airway tube to the backplate, the plaintiff deleted the "tube joint" language from the claims during prosecution. Id. at 1372–73. The plaintiff then argued that the term "backplate" did not include a "tube joint" limitation, while the defendant tried to read the limitation back into the product. Id. The Federal Circuit found that given the plaintiff's voluntary surrender

[8] Plaintiff also cites to the Declaration of Dr. Jennifer Schranz, which was submitted to the PTO during prosecution. This Declaration explicitly states that "prevention of attacks" is "an important part of treatment of HAE," thereby informing the Examiner that "treatment" includes prophylactic care. (Pl.'s Opening Cl. Constr. Br., Ex. E ¶ 6.) Defendant argues that Dr. Schranz's Declaration is not particularly helpful in the discussion of prosecution history disclaimer as it was submitted to the PTO prior to the claim amendment at issue. I disagree with Defendant. Although Dr. Schranz's Declaration does not serve to clearly explain why the "inhibiting, or preventing" language was deleted, it is persuasive in that the PTO was made aware of Plaintiff's understanding that "treating" included prophylactic care, yet chose not to raise that as an issue during the prosecution history.

of the tube joint limitation, "it would be improper to read a tube joint limitation back into the backplate." Id. The court found that devices having tube joints still fell within the claim scope, but were not a required limitation. Id.

Here, by contrast, Defendant's construction would result in a narrowing of the claim scope and preclude methods of prophylactic treatment from falling within that scope. Plaintiff originally intended that its claim include both acute and prophylactic treatment, but deleted the terms "inhibiting" and "preventing" with the understanding that they were inherently included in the term "treating" as defined in the specification. Defendant now wants to read into the '111 patent a limitation that was not otherwise present and was not unambiguously included during the prosecution history. Laryngeal Mask does not provide authority to do so.

In sum, I find no clear and unmistakable disavowal attached to the deletion of the terms "inhibiting" and "preventing" from the original claim 16 of the '111 patent. The Examiner's original rejection of this claim was focused on the level of concentration of the C1-INH injected subcutaneously and not with whether the '111 patent taught acute and/or prophylactic use. Plaintiff amended its claims in order to overcome this obviousness problem in connection with Jiang, as explained in its accompanying submissions to the Examiner. Simultaneously, Plaintiff deleted the terms "inhibiting" and "preventing," choosing to include their meanings within the term "treating." Nothing in the Examiner's rejection or in Plaintiff's responding documents provides any further insight as to the reason for the deletion or otherwise suggests that these terms created an issue with the prior art. At minimum, the events of the prosecution are subject to more than one reasonable interpretation. See SanDisk Corp. v. Memorex Prod., Inc., 415 F.3d 1278, 1287 (Fed. Cir. 2005) ("There is no 'clear and unmistakable' disclaimer if a prosecution argument is subject to more than one reasonable interpretation."). Such ambiguous history cannot undermine

the clear construction already discerned from the claim language and confirmed by the written description.

5. Extrinsic Evidence

Both parties also present various forms of extrinsic evidence to support their proposed constructions. I decline to consider this evidence.

"In most situations, an analysis of the intrinsic evidence alone will resolve any ambiguity in a disputed claim term. In such circumstances, it is improper to rely on extrinsic evidence." Vitronics, 90 F.3d at 1583. In other words, "[i]n those cases where the public record unambiguously describes the scope of the patented invention, reliance on any extrinsic evidence is improper." Id. Rather, the public record of the patentee's claims is comprised of the claims, specification, and file history, and it is that record on which the public and competitors are entitled to rely to ascertain the scope of the patentee's claimed invention. Id. "Allowing the public record to be altered or changed by extrinsic evidence introduced at trial, such as expert testimony, would make this right meaningless." Id.

Here, the proper construction of "treating" is abundantly clear from the patent's explicit definition of the word "treat," the remainder of the specification which describes use of the patented invention for acute and prophylactic use, the dependent claims which describe certain embodiments involving prophylactic use, and the prosecution history which is entirely consistent with the understanding that the word "prevent" is a subset of the word "treat." Accordingly, reference to extrinsic evidence is improper.

6. Conclusion as to "Treating"

For all of the foregoing reasons, I will adopt the construction proposed by Plaintiff and construe the term "treating hereditary angioedema" 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."

B. "U/mL"

The second claim term in dispute is the claim 1 phrase "wherein the administration of the composition comprising the C1 esterase inhibitor increases the level of C1 esterase inhibitor in the blood of the subject to at least about 0.4 U/mL." ('111 patent, col. 13, lines 20–23.) The precise focus of the parties' disagreement centers on the meaning of the term "U/mL." Plaintiff contends that 1 U/mL is "the mean quantity of C1 inhibitor activity present in 1 mL of normal human plasma." Defendant, on the other hand, contends that 1 Unit/mL is "the mean quantity of C1 inhibitor present in 1 mL of normal human plasma." More succinctly, Plaintiff claims that 1 Unit/mL measures the presence of functional C1-INH in the blood, whereas Defendant asserts that it measures only the quantity of C1-INH in the blood.

Reading this term in the context of both the intrinsic and extrinsic evidence cited by the parties, I find Plaintiff's construction of this term to be accurate.

1. The Specification Language

As noted above, the first point of reference in claim construction involves review of the claim language and the surrounding specification.

Defendant offers several citations to the specification in support of its proposed construction. Primarily, Defendant contends that the '111 patent specifically defines 1 Unit/mL as "the mean quantity of C1 inhibitor present in 1 ml of normal human plasma," which indicates that U/mL denotes quantity or amount of C1-INH in the blood. ('111 patent, col. 6, lines 4–6.)

According to Defendant, this is an explicit definition which, under Federal Circuit precedent, should control the claim construction. Moreover, Defendant asserts that this definition is supported by the remainder of the specification, which consistently uses "U/mL" as a measurement of the quantity of C1-INH present in a sample; for example:

- Claim 1 recites the claimed C1-INH to be "administered as a concentration of at least about 400 U/mL," thus reflecting that the concentration is the amount of C1-INH present in the composition. (Id., col. 13, lines 18–19.)

- Table 1 provides "[f]inal concentrations (in U/mL)" of samples containing C1-INH. (Id., col. 8, lines 15–25.)

- The specification states that the "C1 esterase inhibitor level may be kept at or above 0.4 U/mL for at least 50%, at least 75%, at least 90%, at least 95% or more of the time or all of the time . . . ." (Id., col. 6, lines 7–9.)

- The specification describes "concentrations" of C1-INH in measurements of U/mL. (See id. col. 8, lines 1–60; col. 10, lines 35–43.)

Finally, Defendant remarks that the specification never uses U/mL in reference to the activity of C1-INH, suggesting that "U/mL" is a measurement of concentration, not activity.

At first blush, Defendant's proposed construction appears to find support in the language of the patent. But upon review of the specification as a whole, I find, for several reasons, that Plaintiff's proposed construction—which associates U/mL with activity as opposed to concentration levels—is more consistent with the scope and purpose of the patent.

First, although Defendant touts as an explicit definition the specification's language that "1 Unit/ml is the mean quantity of C1 inhibitor present in 1 ml of normal plasma," that language does not appear in the "Definitions" section of the specification. Rather, it is part of a paragraph in the "Detailed Description of the Invention" section and refers only to a "particular embodiment" of the '111 patent. Accordingly, although this language provides guidance regarding the correct construction, it is not a definition which controls my decision. See Katz v. AT&T Corp., 63 F.

Supp. 2d 583, 590 (E.D. Pa. 1999) ("[I]n order for a patentee to assign a special definition to a claim term, he or she must do so clearly in the specification.").

Second, the remainder of the paragraph subsequent to the above language suggests that this language was meant to refer to functionality. The specification discusses the concentration levels of C1-INH in the blood in terms that suggest activity level as opposed to just volume:

> The administration of a 2000 U initial dose of C1 esterase inhibitor followed by 500 U everyday with weekend holidays from administration (i.e., 5 out of 7 days also results in the maintenance of about 0.4 U/ml or higher in blood. Notably, the administration of only the maintenance doses leads to increased and physiologically relevant blood levels of the C1 esterase inhibitor, but delayed compared to those receiving an initial high dose.

('111 patent, col. 6, lines 18–25 (emphasis added).) The term "physiological relevant" connotes activity, as it is "the characteristic of (or corresponding to) healthy or normal biological functioning." (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4475434.) Thus, "increased and physiologically relevant levels of the C1 esterase inhibitor" measured in terms of "U/mL" would necessarily mean levels of active C1-INH.

Third, the specification makes an explicit reference to the Drouet assay as a means of measuring the activity of a C1 esterase inhibitor. ('111 patent, col. 2, line 39–41 (citing Drouet et al. (1988) Clin. Chim. Acta., 174:121–30).) That assay noted that arbitrary units, designated "U/l" were used to express "C1 Inhibitor normal activity" and suggested that "U/l" was a measurement of C1-INH activity or functionality.[9] (Pl.'s Opening Cl. Constr. Br., Ex. Z, 121, 128.) By

[9] Defendant argues that the activity of C1-INH is never actually measured or assayed in '111, thus rendering Drouet irrelevant. The point, however, is that Drouet uses "U/l" as manner of measuring C1-INH activity, meaning that when that unit of measurement is used in the '111, it is referring to C1-INH activity not amount of C1-INH.

referencing this study in the specification, the '111 patent incorporates it—and its definitions—into the specification.

Fourth, the stated purpose of the '111 patent further reveals that U/mL was intended to measure the presence of functional C1-INH in the blood. As set forth in the patent, and as discussed above, HAE is characterized as either type I or type II. Although type I occurs where an individual produces no or low C1-INH, type II exists where the individual has the normal amount of C1-INH, but it is not functioning properly, i.e., not active. ('111 patent, col. 3, lines 56-59.) The specification notes that "the instant invention encompasses methods of treating, inhibiting, and or preventing any condition or disease associated with an absolute or relative deficiency of functional C1 esterase inhibitor." ('111 patent, col. 3, lines 44–47 (emphasis added).) It further provides that: "[t]he restoration of active C1 esterase inhibitor levels in patients having a disorder associated with deficient or reduced levels of active C1 esterase inhibitor (e.g. HAE) is an effective measure for treating such disorders." ('111 patent, col 2, lines 7–10 (emphasis added).) As such, for the invention to properly treat type II HAE—as the specification indicates that it does—the administration of the C1 esterase inhibitor would have to increase not just the quantity or concentration of C1-INH in the blood of a patient, but rather the volume of active or functional C1-INH in the blood. See Osram GmbH v. Int'l Trade Comm'n, 505 F.3d 1351, 1358 (Fed. Cir. 2007) (holding that a construction that is "at odds with the purposes of the invention" was erroneous).

Finally, the specification provides that the compositions of the invention "may be administered, in a therapeutically effective amount, to a patient in need thereof for the treatment of a disorder associated with C1 esterase inhibitor deficiency." (Id., col. 4, lines 2–5.) The Federal Circuit has affirmed a definition of drug concentrations that are "therapeutically effective" as

limiting the claims only to concentrations of the drug "to an extent clinically relevant in the treatment of" the condition at issue. Alcon Research Ltd. v. Apotex, 687 F.3d 1362, 1367 (Fed. Cir. 2012). As therapeutic efficacy with respect to treatment of type II HAE requires restoration of certain levels of active C1-INH, it is logical to read the term "U/mL" to reference activity levels as opposed to weight or volume.

In sum, although the patent does not explicitly define "U/mL" in terms of activity level, the specification provides strong indication that this was the intended meaning. Accordingly, I find that the specification language supports Plaintiff's proposed construction.

2. Prosecution History

Plaintiff's proposed construction finds additional support in the prosecution history of the '111 patent.

During the prosecution of the patent-in-suit, Plaintiff proposed an amendment to claim 1 to overcome the obviousness rejection over Jiang, adding the precise language in dispute here: "wherein the administration of the composition comprising the C1 esterase inhibitor increases the level of C1 esterase inhibitor in the blood of the subject to at least about 0.4 U/mL." ('111 patent, col. 13, lines 20–23.) In support of this amendment, Plaintiff submitted to the Patent Office the Declaration of Dr. Jennifer Schranz under 37 C.F.R. § 1.132 (Mar. 23, 2016).[10] (Pl.'s Opening Cl. Constr. Br, Ex. E.) Dr. Schranz was, at the time, the Vice President of Clinical Development and the Global Development Team Lead for Angioedema at Plaintiff. (Id. ¶ 1.) Dr. Schranz noted that the purpose of the proposed invention was to provide for subcutaneous infusion of C1-INH to

[10] This section provides: "When any claim of an application or a patent under reexamination is rejected or objected to, any evidence submitted to traverse the rejection or objection on a basis not otherwise provided for must be by way of an oath or declaration under this section." Id.

achieve "an appropriate threshold of functional C1-INH activity for routine prophylaxis against angioedema attacks in adolescent and adult patients." (Id. ¶¶ 9–10 (emphasis added).) She remarked that she was "familiar with the animal study described in Jiang, which sought to assess whether reasonable levels of functional human C1-INH could be achieved in swine plasma following [subcutaneous] administration." (Id. ¶ 19 (emphasis added).) Distinguishing the proposed '111 patent by noting that it sought to inject a high concentration formulation of C1-INH—as opposed to the lower concentrations taught in Jiang—Dr. Schranz explained that studies of the proposed patent showed that "injection of 1000 U or more C1-INH at a high concentration (e.g., ~500 U/mL) twice a week would result in maintaining functional C1-INH blood levels above of a threshold level (~0/4 U/mL or 40% of functional C1 INH activity) to achieve therapeutic effects."[11] (Id. ¶ 24 (emphasis added).) Dr. Schranz then referenced a graph regarding the "[p]redicted concentration of functional C1-INH in adult HAE patients receiving twice weekly subcutaneous injection" of the formulation, describing functional C1-INH in terms of "U/mL." (Id. (emphasis added).)

In short, the prosecution history[12] corroborates the interpretation of "U/mL" gleaned from the confines of the specification's language.

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[11] Defendant argues that Dr. Schranz's declaration does nothing more than indicate that a quantitative amount of C1-INH in the blood, expressed as U/mL, can be correlated to a percentage of functional activity without ever stating that U/mL measurement is a functional unit of measure. I find this interpretation of Dr. Schranz's statements to be strained. As noted above, Dr. Schranz repeatedly described the concentration of functional C1-INH blood levels as measured by U/mL.

[12] Defendant asserts that Plaintiff "ignores the myriad of other documents cited during prosecution that confirm that U/mL is a measure of the quantity of C1-INH present in the blood." (Defs.' Answering Cl. Constr. Br. 22.) Three of the cited documents, however, only seek to define one "unit" of C1 esterase inhibitor concentrate (as opposed to 1 U/mL), and note that this measurement is not an international laboratory standard, but merely in "in-house standard" designed to assure lot-to-lot consistency in product potency. (Defs.' Opening Cl. Constr. Br., Ex. 6, at 11; Ex. 21, at 4; Ex. 4, at 189.) The last document, which refers to the drug Cinryze, also describes "[o]ne unit (U) of CINRYZE" as "the mean quantity of C1 esterase inhibitor present in

3. Extrinsic Evidence

In a final effort to support their proposed constructions, both parties cite to various extrinsic evidence. As noted above, where the public record unambiguously describes the scope of the patented invention, reliance on extrinsic evidence is improper. Vitronics, 90 F.3d at 1583. Where the intrinsic record is unclear, however, reliance on extrinsic evidence is appropriate. Intel Corp. v. Broadcom Corp., 172 F. Supp. 2d 515, 527 (D. Del. 2001). A court may look to expert and inventor testimony, dictionaries, and learned treatises. Novartis Corp. v. Teva Pharms. USA, Inc., 565 F. Supp. 2d 595, 607 (D.N.J. 2008). "[B]ecause extrinsic evidence can help educate the court regarding the field of the invention and can help the court determine what a person of ordinary skill in the art would understand claim terms to mean, it is permissible for the district court in its sound discretion to admit and use such evidence. Phillips, 415 F.3d at 1319. In exercising that discretion, however, the court "should keep in mind the flaws inherent in [extrinsic evidence] and assess that evidence accordingly." Id.

Here, while the specification and prosecution history suggest that Plaintiff's construction of the term "U/mL" is correct, I find reference to certain extrinsic evidence useful as further guidance on the field of the invention. For purposes of comprehensiveness, I review the extrinsic evidence and find that it also supports Plaintiff's construction.

a. The World Health Organization Standard

Plaintiff first relies on the World Health Organization ("WHO")'s standard for measuring potency of C1-INH, adopted in 2010. (See Pl.'s Opening Cl. Constr. Br., Ex. Y.) This standard provides a definition of the term "units" as used in measuring C1-INH:

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1 mL of normal fresh plasma," without specifically defining "U/mL." (Def.'s Opening Cl. Constr. Br., Ex. 7, at 7.) That document also goes on to note that the "units" referred to are "functionally active C1 esterase inhibitor." (Id.)

Units

> Diagnostic plasma samples and purified therapeutic products are currently assigned potency values[13] relative to commercial or internal standards and 1 U is defined as the amount of C1-inh present in 1 ml of normal plasma. It is therefore proposed that the IU [international unit] is also defined in this way for continuity and consistency with current labelling practice.

(Id. at 2–3 (emphasis added).) The standard goes on to note that C1-INH potency values are measured as 1.0 international unit per ml. (Id.)

The identical language is present in the '111 patent, which it states that "1 Unit/ml is the mean quantity of C1 inhibitor present in 1 ml of normal human plasma." ('111 patent, col. 6, lines 4–6.) Construing this language as an adoption[14] of WHO's standard, "U/mL" as used in the '111 patent should similarly be defined as a measurement of the potency or activity of the C1-INH in the blood, as opposed to simply the weight or amount of C1-INH in the blood. As such, this source supports Plaintiff's proposed definition.

b. Dr. MacGinnitie

Plaintiff also proffers a Declaration by Dr. Andrew MacGinnitie's Declaration a clinical director of the Division of Immunology, attending physician at Boston Children's Hospital, and Associate Professor of Pediatrics at Harvard Medical School. (MacGinnitie Decl. ¶ 6.) According to Dr. MacGinnitie:

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[13] The Food and Drug Administration defines "potency" as "the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result." 21 C.F.R. § 600.3(s).

[14] Plaintiff contends that the '111 expressly incorporates the WHO standard for measuring potency and, therefore, this standard is part of the intrinsic evidence. I disagree. Although the specification uses the same language as the WHO standard, thus signaling an intent to ascribe the same meaning to that language, the specification neither explicitly cites nor incorporates by reference the WHO standard.

> It is well understood that levels of C1-INH in the blood should be measured by C1-INH activity as opposed to C1-INH weight, because . . . some forms of HAE (e.g., HAE Type II) are characterized by already–present but inactive C1-INH. Indeed, the total weight of C1-INH, active and inactive, in the blood of patients with Type II HAE is normal or even elevated. A measure of the weight of C1-INH would thus capture the dysfunctional C1-INH in a Type II HAE patient, rendering the weight measurement meaningless in terms of diagnosing HAE or determining whether sufficient amounts of active C1-INH have been provided to a patient (and thus are present in the patient's blood) to have a therapeutic effect. The '111 patent specification expressly describes treating both Type I and Type II HAE. Col 3, lns. 55-56 ("[i]n a particular embodiment, the hereditary angioedema is type I or type II"). In addition, claim 6 expressly states that the invention includes "[t]he method of claim 1, wherein the HAE is Type I HAE or Type II HAE."

(Id. ¶ 42.) Dr. MacGinnitie thus opines that a person of ordinary skill in the art would understand the terms "a concentration of at least about 400 U/mL" and "a dose of at least about 1000 U," which also appear in claim 1 of the '111 patent, to describe measures of C1-INH activity using the World Health Organization standard for Units. (Id. ¶ 44.)

While this Declaration is marginally instructive "to confirm that the construed meaning is consistent with the denotation ascribed by those in the field of the art," Omega Eng'g, Inc. v. Raytek Corp., 334 F.3d 1314, 1332 (Fed. Cir. 2003) (internal quotations omitted), the Federal Circuit has cautioned that "extrinsic evidence consisting of expert reports and testimony is generated at the time of and for the purpose of litigation and thus can suffer from bias that is not present in intrinsic evidence." Phillips, 415 F.3d at 1318.

Cognizant of these principles, I find that Dr. MacGinnitie's Declaration bolsters the construction inherent in the instrinsic evidence, but I otherwise accord it limited weight.[15]

[15] Defendant offers several challenges to Dr. MacGinnitie's Declaration based on the evidence upon which he relies. As these challenges are similar to the arguments Defendant put forth above in support of its construction, I need not address them again in detail here.

c. Other Studies

In an effort to rebut Plaintiff's construction, Defendant cites to several other studies to argue that C1-INH activity is routinely measured through a functional chromographic assay and is expressed as a percentage of normal human values, as opposed to being expressed in terms of U/mL. (See Def.'s Opening Cl. Constr. Br., Ex. 29, Inmaculada Martinez-Saguer, et al., Pharmacokinetics of Plasma-Derived C1-Esterase Inhibitor After Subcutaneous Versus Intravenous Administration in Subjects with Mild or Moderate Hereditary Angioedema: the Passion Study, 54 Transfusion Practice 1552, 1554, 1556 (2014) ("C1-INH activity was determined using the functional chromogenic assay . . . . Standard human plasma served as the calibrator; the results are expressed as percentage of normal values."); Ex. 30, Bruce Zuraw, et al., Recombinant Human C1-Inhibitor for the Treatment of Acute Angioedema Attacks in Patients with Hereditary Angioedema, 126 J. Allergy Clin. Immunol. 821, 822, 824 (2010) ("Functional C1 INH activity was assessed with a chromogenic assay and expressed as a percentage of normal. Protein levels of C1 INH and C4 were measured with nephelometric assays and C1q with ELISA").)

As aptly noted by Dr. MacGinnitie, however, a person of ordinary skill in the art would understand that percentages, or U/mL, are both used to describe activity. (MacGinnitie Supp. Decl. ¶ 29.) Indeed, as a matter of logic, percentages and U/mL (e.g., 40% and 0.4 U/mL) are interchangeable terms, as is reflected in much of the intrinsic evidence.[16]

More importantly, I recognize that both parties have reached into the "virtually unbounded universe of potential extrinsic evidence of some marginal relevance" in order to find studies that

[16] See Colm Farrell, et al., Population Pharmacokinetics of Recombinant Human C1 Inhibitor in Patients with Hereditary Angioedema, Br. J. Clin. Pharmacol. (2013) (discussing measurement of levels of functional C1 INH primarily in terms of both U/mL, but interchangeably using percentage values).

support their proposed constructions, some of which use U/mL as a measure of activity and some of which use percentages as a measure of activity. Phillips, 415 F.3d at 1318. Cognizant of the fact that a court should not rely on extrinsic evidence to change of the meaning of claims in derogation of the intrinsic evidence, I find these studies unpersuasive.

4. Conclusion as to "U/mL"

In light of the foregoing, I will adopt the construction proposed by Plaintiff and construe the term "U/mL" as **"the mean quantity of C1 inhibitor activity present in 1 mL of normal human plasma."** To construe the claim without the word activity would render it inconsistent with the purpose of the '111 patent in treating both Type I and Type II angioedema, would disregard the language of the specification, and would conflict with the prosecution history and relevant extrinsic evidence.

IV. CONCLUSION

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