IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

FOREST LABORATORIES INC., ET AL.,	:	
	:	
Plaintiffs,	:	
	:	
v.	:	C.A. No. 08-21-GMS-LPS
	:	CONSOLIDATED
COBALT LABORATORIES INC., ET AL.,	:	
	:	
Defendants.	:	

REPORT AND RECOMMENDATION
REGARDING CLAIM CONSTRUCTION

This is an ANDA patent infringement action. Plaintiffs – Forest Laboratories, Inc., Forest Laboratories Holdings Ltd., Merz Pharma GmbH & Co. KgaA, and Merz Pharmaceuticals GmbH (collectively "Plaintiffs") – assert that Defendants' proposed generic versions of Plaintiffs' branded drug, NAMENDA, infringe Plaintiffs' U.S. Patent No. 5,061,703 ("'703 patent"), entitled "Adamantane Derivatives in the Prevention and Treatment of Cerebral Ischemia." This is my recommended construction of the disputed claim terms.

BACKGROUND

A. Procedure

On October 17, 2008, Plaintiffs and Defendants – Cobalt Laboratories, Inc., Dr. Reddy's Laboratories, Inc., Dr. Reddy's Laboratories Ltd., Interpharm Holdings, Inc., Interpharm, Inc., Genpharm ULC, Genpharm, L.P., Mylan Pharmaceuticals Inc., Lupin Pharmaceuticals, Inc., Lupin Ltd., Orchid Pharmaceuticals Inc., Orchid Chemicals & Pharmaceuticals Ltd., Orgenus Pharma Inc., Sun Pharmaceuticals Indus. Ltd., Teva Pharmaceuticals USA, Inc., Upsher-Smith

Laboratories, Inc., Wockhardt USA Inc., Wockhardt Limited, Amneal Pharmaceuticals of New York LLC, and Amneal Pharmaceuticals LLC, as well as Apotex Inc. and Apotex Corp. (these last two referred to together as "Apotex") – filed a Joint Claim Chart identifying the claim terms the parties contend require construction. (D.I. 198)[1] Because various subsets of Defendants sometimes propose different constructions than other Defendants, I will use "Majority Defendants" to refer to the position advocated by a majority of the Defendants with respect to any particular term under discussion.

The parties briefed their positions on claim construction and, on December 15, 2008, I conducted a Markman hearing. *See* Dec. 15, 2008 Hearing Transcript (D.I. 248) ("Tr."). The terms in dispute and requiring construction relate to Claims 1, 10, 11, 13, 14, and 17 of the '703 patent.

B. The '703 Patent

The Reexamination Certificate for the '703 patent issued on November 7, 2006. (JA10)[2] The patent contains three independent claims and 16 dependent claims. The claims at issue are reproduced below, with emphasis added to show the disputed claim terms.[3]

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[1]Unless otherwise indicated, all Docket Index ("D.I.") references hereinafter are to C.A. 08-21-GMS-LPS.

[2]References to the "Joint Appendix of Intrinsic and Extrinsic Evidence Cited in the Parties' Claim Construction Briefs" are indicated by "JA" and the applicable page number. Except where the exhibit being referenced is Exhibit A, the Exhibit number is also indicated.

[3]The Reexamination Certificate italicizes the portions of the claims that were added during the reexamination. This emphasis has been omitted here.

Independent Claim 1 reads:

> A method for the ***prevention*** or ***treatment*** of ***cerebral ischemia*** comprising the step of orally administering, to a ***patient diagnosed with Alzheimer's disease*** and ***in need thereof***, an ***effective amount*** of an adamantane derivative of the general formula . . . .

(JA12 at col. 1 lines 26-31)

Dependent Claim 10:

> A method according to claim 1 for the ***treatment*** of ***Alzheimer's disease*** wherein said adamantane derivative is memantine and said effective amount is from about 0.01 to 100 mg/kg.

(JA12 at col. 1 lines 61-64)

Dependent Claim 11:

> A method of claim 1, wherein the adamantane derivative is administered in an ***effective cerebral ischemia-alleviating or preventive amount***.

(JA8 at col. 14 lines 45-47)

Dependent Claim 13:

> A method of claim 11, wherein the adamantane derivative is administered in an ***amount effective to prevent degeneration and loss of nerve cells after ischemia***.

(JA8 at col. 14 lines 52-55)

Independent Claim 14:

> A method for the ***treatment*** of ***cerebral ischemia*** comprising orally administering to a ***patient diagnosed with Alzheimer's disease*** and ***in need of such treatment*** an ***effective amount*** of an adamantane derivative of the general formula . . . .

(JA12 at col. 1 lines 65-67 to col. 2 lines 1-2)

Independent Claim 17:

> A method for the ***treatment*** of an ***imbalance of neuronal stimulation after Alzheimer's disease***, comprising orally administering to a ***patient diagnosed with Alzheimer's disease*** and ***in need of such treatment*** an ***effective amount*** of an adamantane derivative of the general formula . . . .

(JA12 col. 2 lines 32-36)

LEGAL STANDARDS

"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 v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (internal quotation marks omitted). Construing the claims of a patent is a question of law. *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 977-78 (Fed. Cir. 1995), *aff'd*, 517 U.S. 370, 388-90 (1996). "[T]here is no magic formula or catechism for conducting claim construction." *Phillips*, 415 F.3d at 1324. Instead, the court is free to attach the appropriate weight to appropriate sources "in light of the statutes and policies that inform patent law." *Id.*

"[T]he words of a claim are generally given their ordinary and customary meaning . . . [which 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." *Id.* at 1312-13 (internal citations and quotation marks omitted). "[T]he ordinary meaning of a claim term is its meaning to the ordinary artisan after reading the entire patent." *Id.* at 1321 (internal quotation marks omitted). The patent specification "is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term." *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996).

While "the claims themselves provide substantial guidance as to the meaning of particular claim terms," the context of the surrounding words of the claim also must be considered. *Phillips*, 415 F.3d at 1314. Furthermore, "[o]ther 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 . . . ." *Id.* (internal citation omitted).

It is likewise true that "[d]ifferences 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 (internal citation omitted). 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).

It is also possible that "the specification may reveal a special definition given to a claim term by the patentee that differs from the meaning it would otherwise possess. In such cases, the inventor's lexicography governs." *Phillips*, 415 F.3d at 1316. It bears emphasis that "[e]ven when the specification describes only a single embodiment, the claims of the patent will not be read restrictively unless the patentee has demonstrated a clear intention to limit the claim scope using words or expressions of manifest exclusion or restriction." *Liebel-Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 906 (Fed. Cir. 2004) (internal quotation marks omitted), *aff'd*, 481 F.3d 1371 (Fed. Cir. 2007).

In addition to the specification, a court "should also consider the patent's prosecution history, if it is in evidence." *Markman*, 52 F.3d at 980. The prosecution history, which is

"intrinsic evidence," "consists of the complete record of the proceedings before the PTO [Patent and Trademark Office] and includes the prior art cited during the examination of the patent." *Phillips*, 415 F.3d at 1317. "[T]he prosecution history can often inform the meaning of the claim language by demonstrating how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution, making the claim scope narrower than it would otherwise be." *Id.*

A court also may rely on "extrinsic evidence," which "consists of all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises." *Markman*, 52 F.3d at 980. For instance, technical dictionaries can assist the court in determining the meaning of a term to those of skill in the relevant art because such dictionaries "endeavor to collect the accepted meanings of terms used in various fields of science and technology." *Phillips*, 415 F.3d at 1318. In addition, expert testimony can be useful "to ensure that the court's understanding of the technical aspects of the patent is consistent with that of a person of ordinary skill in the art, or to establish that a particular term in the patent or the prior art has a particular meaning in the pertinent field." *Id.* Nonetheless, courts must not lose sight of the fact that "expert reports and testimony [are] generated at the time of and for the purpose of litigation and thus can suffer from bias that is not present in intrinsic evidence." *Id.* Overall, while extrinsic evidence "may be useful" to the court, it is "less reliable" than intrinsic evidence, and its consideration "is unlikely to result in a reliable interpretation of patent claim scope unless considered in the context of the intrinsic evidence." *Id.* at 1318-19.

Finally, "[t]he 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 PLC v. Marposs Societa' per Azioni, 158 F.3d 1243, 1250 (Fed. Cir. 1998). It follows that "a claim interpretation that would exclude the inventor's device is rarely the correct interpretation." *Osram GmbH v. Int'l Trade Comm'n*, 505 F.3d 1351, 1358 (Fed. Cir. 2007). Thus, if possible, claims should be construed to uphold validity. *See In re Yamamoto*, 740 F.2d 1569, 1571 (Fed. Cir. 1984).

CONSTRUCTION OF THE DISPUTED TERMS

A. "Cerebral ischemia"

The parties' first dispute concerns the term "cerebral ischemia," which appears in Claims 1 and 14. Plaintiffs propose that "cerebral ischemia" should be construed as "an imbalance of neuronal stimulation mechanisms." Plaintiffs assert that this construction is proper because the patentee was its own lexicographer; that is, the Plaintiffs' proposed construction is the definition that the patentee gave "cerebral ischemia" in the patent specification. (D.I. 223 at 2)

The Majority Defendants propose that "cerebral ischemia" should be construed as what they contend is its plain and ordinary meaning: "An acute interruption of blood supply to the brain characterized by a destruction of brain cells." To the extent the "destruction of brain cells" is a consequence of cerebral ischemia, and not strictly speaking part of cerebral ischemia, the Majority Defendants insist on including this within the construction because one of ordinary skill in the art reading the patent would understand that such brain cell destruction is part of the context of how the term is being used. (Tr. at 108-09)

Defendant Apotex also proposes that "cerebral ischemia" should be construed according to its plain and ordinary meaning, but what Apotex posits as the plain and ordinary meaning of the term differs from the meaning proposed by the Majority Defendants. Apotex proposes to

construe "cerebral ischemia" as "an acute interruption of blood supply to the brain." In Apotex's view, the death of brain cells, which the Majority Defendants' construction requires, is a consequence of cerebral ischemia (one of many consequences), but it is not part of cerebral ischemia. On this point the Plaintiffs are in agreement with Apotex.

According to Plaintiffs, choosing between their construction and Defendants' proposed constructions turns largely on determining whether the patent relates to a problem of neuronal imbalance, as Plaintiffs contend, or instead deals essentially with a problem of blood supply to the brain, as Defendants' constructions imply. Plaintiffs acknowledge that the term "ischemia" has a plain and ordinary meaning to one of ordinary skill in the art having to do with an interruption in blood flow. (Tr. at 40-41) However, Plaintiffs insist that, in the context of the patent specification, it is clear that the patentee was using the term "cerebral ischemia" not to refer to an interruption in blood supply to the brain (i.e., cerebrum) but, instead, to refer to an imbalance of neuronal stimulation mechanisms.

According to Plaintiffs, one of ordinary skill in the art reading the entire patent would understand "that memantine acts on the NMDA [–methyl D-aspartate] receptor to deal with the neuronal imbalance. It does not act on blood flow." (Tr. at 14) Plaintiffs assert, therefore, that "the basic dispute between the parties is did the patent invent compounds, chemicals, directed to interfere with calcium ions through the NMDA receptor or did the patent invent chemical compounds that prevent the interruption of blood flow?" (Tr. at 20)

The Defendants, by contrast, argue that the issue requiring decision is not the broad question of whether the patent relates to nueronal activities or blood supply. Rather, the issue is whether the patentee met its burden of establishing that the patent used the term "cerebral

ischemia" in some manner other than its plain and ordinary meaning. To the Majority Defendants, "the nub of the dispute" is "did the plaintiffs act with sufficient deliberateness and clarity such that they told readers that when they're talking about the word 'cerebral ischemia,' they are excluding from the definition the very essence of cerebral ischemia, which is the stoppage of blood flow." (Tr. at 90) To answer this question, one must first look at the pertinent parts of the specification and then "look at the rest of the specification and the intrinsic record and see if [the Plaintiffs'] argument really makes sense." (Tr. at 90-91)

I agree that the Defendants have properly framed the question presented, but I have concluded that Plaintiffs' answer is the correct one. Looking at how "cerebral ischemia" is used in the specification, and then considering the remainder of the specification and the intrinsic evidence, I find that the patentee defined "cerebral ischemia" with sufficient and "reasonable clarity, deliberateness, and precision" in the manner Plaintiffs propose. *Abbott Labs. v. Syntron Bioresearch, Inc.*, 334 F.3d 1343, 1354 (Fed. Cir. 2003) (internal quotation marks and emphasis omitted).

I reach this conclusion first by looking at how the patent specification uses the disputed term "cerebral ischemia." *See generally ICU Medical, Inc. v. Alaris Medical Systems, Inc.*, 558 F.3d 1368, 1374 (Fed. Cir. 2009) (stating that because person having ordinary skill in art is deemed to read claim term in context of entire patent, including specification, "not only is th[is] written description helpful in construing claim terms, but it is also appropriate to rely heavily on the written description for guidance as to the meaning of the claims") (internal quotation marks omitted). The first two uses – in the Abstract and then the first sentence of the patent – do not tell one much that is helpful to resolving the parties' dispute. The Abstract begins by stating that

the '703 patent discloses "[a] method for the prevention and treatment of ***cerebral ischemia*** using an adamantane derivative" of a formula. (JA1 (emphasis added)) The patent then begins with the statement: "The present invention relates to a method for the prevention or treatment of ***cerebral ischemia*** using an adamantane derivative" of a disclosed general formula. (JA2 at col. 1 lines 6-8 (emphasis added))

The patent goes on to state:

> The compounds according to formula (I) known from the above-cited patents have so far been used for the treatment of parkinsonian and parkinsonoid diseases. Their mode of action is attributed to a dopaminergic influence on the CNS [central nervous system] . . . .
>
> In contrast to this type of disease, ***cerebral ischemia*** is characterized by a pathophysiological situation defined by an imbalance of neuronal stimulation mechanisms. In this context, the excessive inflow of calcium through NMDA receptor channels finally leads to the destruction of brain cells in specific brain areas . . . .
>
> Therefore, in order to treat or eliminate this pathological situation, an antagonistic intervention is required with regard to the NMDA receptor channels . . . .
>
> The present invention is aimed at preparing and employing compounds which can be chemically generated by simple methods, exhibiting an NMDA receptor channel-antagonistic and anticonvulsive action, for use in the prevention and treatment of ***cerebral ischemia***.

(JA2-3 at col. 2 lines 38-68 to col. 3 lines 1-3 (emphasis added; internal citations to prior art omitted))

The main points derived from these portions of the specification are that the invention has to do with the central nervous system and not the bloodstream; the problem the invention is directed to addressing is an imbalance of neuronal stimulation mechanisms; and the invention acts on NMDA receptor channels. All of these points support the Plaintiffs' construction and

detract from the proposed constructions of the Defendants.

The patent's next use of "cerebral ischmia" is in the following context:

> It has been found unexpectedly that the use of these compounds prevents an impairment or further impairment, i.e., degeneration and loss of nerve cells, after ischemia. Therefore, the adamantane derivatives of formula (I) are especially suited for the prevention and treatment of ***cerebral ischemia*** after apoplexy, open-heart surgery, cardiac standstill, subarachnoidal homorrhage, transient cerebro-ischemic attacks, perinatal asphyxia, anoxia, hypoglycemia, apnoea and Alzheimer's disease. The amount employed is a ***cerebral-ischemia***-alleviating or preventive amount.

(JA3 at col. 3 lines 7-17 (emphasis added)) Here, one of ordinary skill in the art would note the distinction between "ischemia," which has a plain and ordinary meaning relating to an interruption in blood supply, and "cerebral ischemia," which is being used, in context, to refer to a neuronal imbalance.[4]

The next use of the term "cerebral ischemia" appears in describing prior art in connection with reporting the results of a pharmacological test. The patent states: "PCP has been shown to prevent the destruction of brain cells after ***cerebral ischemia*** in rats (Sauer et al., Neurosci. Lett. 91, 1988, 327, 332)." (JA3 at col. 4 lines 59-62 (emphasis added)) The study being referred to is not in the record before me. On its face, I am unable to find anything in this use of the term in the specification that undermines the Plaintiffs' construction.

The specification goes on to use "cerebral ischemia" in describing two additional

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[4]Even if, in this portion of the specification, the patentee was using "ischemia" as a shorthand for "cerebral ischemia" – and, hence, "ischemia" should be read in this portion of the patent to refer to neuronal mechanisms and not blood supply – that would not undermine the conclusion that "cerebral ischemia" refers to neuronal mechanisms. That is, ambiguity in the patentee's use of the term "ischemai" does not necessarily lead to the conclusion that the patentee's use of the separate term "cerebral ischemia" is ambiguous.

pharmacological tests.[5] Example E is referred to by the caption "Protection Against ***Cerebral Ischemia***." (JA4 at col. 6 line 27 (emphasis added)) The patent describes how in Example E the carotid arteries of rats are occluded and blood is withdrawn; thereafter this "ischemia is terminated by opening the carotids and reinfusion of the withdrawn blood." (JA4 at col. 6 lines 28-33) Clearly, here "ischemia" is being used in its plain and ordinary sense – to refer to an interruption in the supply of blood to the brains of the rats – as Plaintiffs acknowledge. (Tr. at 177)[6] The patent goes on to state that the results of Example E "show . . . reduction of the post-ischemic neuronal brain damage." (JA4 at col. 6 lines 52-53) Again, ischemia ("ischemic") is being used here to refer to an interruption in the blood supply. Nevertheless, the discussion of Example E also notes "the results show that the compounds according to formula (I) exhibit a neuroprotective action in ***cerebral ischemia***." (JA4 at col. 6 lines 58-60 (emphasis added))

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[5]More generally, and again supportive of Plaintiffs' construction, the specification describes several "pharmacological tests" establishing "[t]he efficacy of the compounds of formula (I)." (JA3 at col. 4 lines 52-53) Each of these tests relates to NMDA receptors; none relates to the bloodstream. *See* A (concluding compound "binds to NMDA receptor channels at the same site as the NMDA antagonist PCP") (JA4 at col. 5 lines 6-8); B ("[D]erivatives of formula (I) are able to block the NMDA receptor channel as has been described for PCP . . . .") (JA4 at col. 5 lines 41-42); C ("[D]erivatives of formula (I) exhibit a protective effect against electrically induced convulsions.") (JA4 at col. 6 lines 12-13); D ("[T]here is a correlation between the blocking of the NMDA receptor channel and the anticonvulsive action of the adamantanes of formula (I).") (JA4 at col. 6 lines 22-25); E (showing "reduction of the post-ischemic neuronal brain damage") (JA4 at col. 6 lines 52-53); F ("[D]erivatives of the present invention are protective against the NMDA-induced mortality.") (JA5 at col. 7 lines 7-9); G (results indicate "a specific interaction with the NMDA receptor channel and predict[] neuroprotective properties") (JA5 at col. 7 lines 37-39).

[6]In their briefing, Plaintiffs had argued that "ischemia" as used in Example E means "*i.e.* 'an imbalance of neuronal stimulation mechanisms.'" (D.I. 235 at 8) This is incorrect. "Ischemia" as so construed in the context of Example E would be nonsensical. Moreover, it would mean that "ischemia" and "cerebral ischemia" mean the same thing, which, in context, they do not. At the hearing, Plaintiffs acknowledged that "ischemia" as used in this portion of the specification's discussion of Test E refers to the interruption of blood supply. (Tr. at 177)

Here, it appears that "cerebral ischemia" is being used in a manner distinct from "ischemia;" that is, "cerebral ischemia" does not refer to an interruption in blood supply, even as "ischemia" alone does.

With respect to Example F, the patent states: "It is well known that, subsequent to ***cerebral ischemia***, glutamate and aspartate levels increase massively in the brain." (JA4 at col. 6 lines 66-68 (emphasis added)) Defendants suggest that in this sentence "cerebral ischemia" must refer to an interruption of blood supply; because glutamate and aspartate are neurons, taking the Plaintiffs' construction would have the sentence effectively read "subsequent to an imbalance of neuronal stimulation one gets an imbalance of neuronal stimulation." *See* Tr. at 96-97, 196. In context, however, I believe even in Example F the patentee was using "cerebral ischemia" to refer to a neuronal condition and not to an interruption of blood supply. Substituting Plaintiffs' proposed construction in this sentence yields a true, and comprehensible, sentence: "It is well known that, subsequent to an imbalance of neuronal stimulation, glutamate and aspartate levels increase massively in the brain." (Tr. at 174) As importantly, the conclusion of Example F – "We have found that the adamantane derivatives of the present invention are protective against the NMDA-induced mortality" (JA5 at col. 7 lines 7-9) – does not make sense if "cerebral ischemia" is referring to a blood event as opposed to a neuronal event.

In the final uses of "cerebral ischemia" (other than in the claims), the patent specification states:

> It is thus seen that certain adamantane derivatives, some of which are novel, have been provided for the prevention and treatment of ***cerebral ischemia***, and that pharmaceutical compositions embodying such an adamantane derivative have been provided for use in the prevention and treatment of ***cerebral ischemia***, the amount of the said adamantane derivative provided in either case being a ***cerebral***

ischemia-alleviating or preventive amount.

(JA8 at col. 13 lines 34-42) In this sentence, as with the first two uses of "cerebral ischemia" (in the Abstract and at the start of the patent), there is no strong support for either side's construction. But, clearly, nothing about the use of "cerebral ischemia" here detracts from Plaintiffs' proposed construction or enhances that of Defendants.

Therefore, in the context of the specification, "cerebral ischemia" refers to a neuronal situation and not to an interruption in blood supply. As for the specific meaning that is accorded to "cerebral ischemia," I agree with Plaintiffs that it should be "an imbalance of neuronal stimulation mechanisms." In the patent specification, the patentee stated that "cerebral ischemia is characterized by a pathophysiological situation defined by an imbalance of neuronal stimulation mechanisms." (JA2 at col. 2 lines 46-48) The phrase "is characterized by" may, as here, be sufficient to call out to one of ordinary skill in the art that a claim term is being defined for purposes of the patent. *See generally Agere Systems Inc. v. Atmel Corp.*, 2003 WL 21652264, at *18-19 (E.D. Pa. May 27, 2003) (concluding patentee was own lexicographer where patentee wrote, "'The self-limiting effect is characterized by a tungsten formation rate at 10 minutes that is less than 10% of the initial equilibrium rate.'"). During the reexamination proceedings, the patentee expressly identified this portion of the specification as providing the proper construction of "cerebral ischemia," writing:

> As defined in the '703 patent, "cerebral ischemia" refers to an imbalance of neuronal stimulation in which an excessive influx of calcium through NMDA receptor channels leads to degeneration and loss of brain cells (col. 2, lines 46-51). This imbalance can be initiated by various conditions, including Alzheimer's disease (col. 3, lines 10-16), and is characterized by a substantial increase in excitatory amino acids, which allows for an excessive influx of calcium through NMDA receptor channels leading to loss of brain cells (col. 2, lines 46-52).

(JA0760-61) Contrary to Defendants' suggestion that this statement should be accorded little significance, *see* Tr. at 104, 125, the reexamination proceedings are part of the intrinsic evidence on which the Court may rely. *See generally Procter & Gamble Co. v. Kraft Foods Global, Inc.*, 549 F.3d 842, 848 (Fed. Cir. 2008) ("The district court should monitor the [reexamination] proceedings before the PTO to ascertain whether its construction of any of the claims has been impacted by further action at the PTO or any subsequent proceedings."); *Alloc, Inc. v. Norman D. Lifton Co.*, 2007 WL 2089303, at *11 (S.D.N.Y. July 18, 2007) ("A patent's prosecution history during a reissue or re-examination proceeding is part of the intrinsic evidence of claim meaning . . . ."); *Creo Products Inc. v. Presstek, Inc.*, 166 F. Supp.2d 944, 963 n.31 (D. Del. 2001) (stating request for reexamination is part of intrinsic evidence), *aff'd*, 305 F.3d 1337 (Fed. Cir. 2002). I find the patentee's statement important because it shows the patentee telling the PTO exactly what Plaintiffs are now advocating in Court. That the PTO issued the Reexamination Certificate for the claims without indicating any disagreement with the patentee's definition of "cerebral ischemia" is important intrinsic evidence supporting Plaintiffs' proposed construction.

Defendants raise several other objections to Plaintiffs' construction but none, individually or collectively, convince me that Plaintiffs' construction should be rejected. Defendants point to a portion of the prosecution history in which the inventors defined "ischemia" as "insufficient blood supply to an organ." (JA131) As Plaintiffs point out, this definition appears in a discussion of prior art, and there is no dispute that some of the prior art uses "ischemia" consistent with its plain and ordinary meaning. More importantly, this is a definition of

"ischemia," not of "cerebral ischemia."[7] As already noted, there are places even in the patent specification where "ischemia" is used in its plain and ordinary sense as relating to an interruption in blood supply. But nowhere is "cerebral ischemia" used to refer to an interruption in blood supply. Defendants also contend that Plaintiffs' construction must be wrong because it is broad enough to capture all types of neuronal imbalances, including Parkinson's disease, yet the specification explicitly contrasts cerebral ischemia with Parkinson's. *See* JA2 at col. 2 lines 38-48. Yet this concern is eliminated if, as I recommend below, Plaintiff's construction of "imbalance of neuronal stimulation" is adopted. (Tr. at 100) (counsel for Majority Defendants conceding this point) Finally, Defendants insist that Plaintiffs' construction would result in the reexamined claims having broader scope than the original claims, which would render the claims of the '703 patent invalid pursuant to 35 U.S.C. § 305. I do not perceive a need to reach this invalidity argument at this time. *See Ampex Corp. v. Eastman Kodak Co.*, 460 F. Supp.2d 541, 543 n.1 (D. Del. 2006) ("The validity of a claim is not an issue of claim construction . . . . I will not convert Defendants' claim construction argument into a motion for summary judgment.").

Finally, I agree with Plaintiffs and Apotex that the destruction of brain cells that is a consequence of cerebral ischemia is not itself part of cerebral ischemia and, therefore, should not be part of the Court's construction of the term "cerebral ischemia." *See* JA2 at col. 2 lines 46-52 ("In contrast to this type of disease, cerebral ischemia is characterized by a pathophysiological

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[7]The same "Definitions" page on which the definition of "ischemia" is provided goes on to state: "In connection with dementia research, animal models of cerebral ischemia have recently been introduced. By brief interruption of cerebral blood supply selective degeneration of nerve cells is induced which can be identified and evaluated microsopically about 8 days after recirculation." (JA131) This statement, which is expressly not given as a definition, does not appear to help either side's claim construction argument.

situation defined by an imbalance of neuronal stimulation mechanisms. In this context, the excessive inflow of calcium through NMDA receptor channels ***finally leads*** to the destruction of brain cells in specific brain areas.") (emphasis added; internal citations omitted).

Thus, I recommend that the Court construe "cerebral ischemia" to mean "an imbalance of neuronal stimulation mechanisms."

B. "Prevention of cerebral ischemia"

The next term in dispute is "prevention of cerebral ischemia." The proper construction follows from the construction of "cerebral ischemia." I recommend that this term be construed as "prevention of an imbalance of neuronal stimulation mechanisms."

Plaintiffs propose that "prevention of cerebral ischemia" be construed as "prevention of impairment or further impairment, *i.e.*, degeneration and loss of nerve cells, after cerebral ischemia," with "cerebral ischemia" defined as I have recommended above. Plaintiffs contend that the patentee defined this term. *Id.* For support, they point to the following specification statement: "It has been found unexpectedly that the use of these compounds prevents an impairment or further impairment, i.e., degeneration and loss of nerve cells, after ischemia." (JA3 at col. 3 lines 7-10) I do not agree with Plaintiffs that this specification statement clearly, deliberately, and precisely defines "prevention of cerebral ischemia." If this statement is defining anything, it seems to be defining "impairment" – as "degeneration and loss of nerve cells, after ischemia" – and not defining "prevention of cerebral ischemia." Moreover, the specification statement on which Plaintiffs rely references "ischemia," not "cerebral ischemia."

The Defendants' proposed constructions, however, are no more persuasive. The Majority Defendants propose that "prevention of cerebral ischemia" be construed as "prevention of the

destruction of brain cells that results from an acute interruption of blood supply to the brain." Having rejected the Majority Defendants' proposed construction of "cerebral ischemia," there is nothing to recommend adopting their construction of "prevention of cerebral ischemia." Even the Majority Defendants concede that they have not proposed the plain and ordinary meaning of the term, which would be something like the "prevention of an acute interruption of blood flow to the brain." *See* Tr. at 199-200.

Apotex, by contrast, does propose to construe "prevention of cerebral ischemia" consistent with its plain and ordinary meaning, as "prevention of an acute interruption of blood supply to the brain." (D.I. 222 at 12 n.5) However, for the same reasons I recommend rejecting Apotex's proposed construction of "cerebral ischemia," I likewise recommend rejecting Apotex's proposed construction of "prevention of cerebral ischemia." Fundamentally, the '703 patent discloses an invention that works on neuronal activity, not on blood flow. Thus, one of ordinary skill in the art would not read "prevention of cerebral ischemia" in the context of the '703 patent to refer to "prevention of an acute interruption of blood supply to the brain."

Therefore, I recommend that "prevention of cerebral ischemia" be construed as "prevention of an imbalance of neuronal stimulation mechanisms."

C. "Treatment of cerebral ischemia"

Plaintiffs propose that "treatment of cerebral ischemia" be construed as "an antagonistic intervention with regard to the N-methyl-D-aspartate (NMDA) receptor channels." According to Plaintiffs, here, again, the patentee was its own lexicographer. (D.I. 223 at 2) Plaintiffs contend that this term is defined in the portion of the specification which states: "in order to treat or eliminate this pathological situation, an antagonistic intervention is required with regard to the

NMDA receptor channels." (JA2 at col. 2 lines 53-55)

The Majority Defendants would instead have the Court construe "treatment of cerebral ischemia" as "stopping the destruction of brain cells that results from an acute interruption of blood supply to the brain." They insist that the specification statement on which Plaintiffs rely is not a definition but merely "where the patent owner is explaining to you the mechanism of action." (Tr. at 113)

I agree with Plaintiffs' construction. In context, the specification statement on which Plaintiffs rely is sufficiently clear, deliberate, and precise to define what the patentee meant by "treatment" of the pathological situation of "cerebral ischemia." In the context of the '703 patent, "treatment of cerebral ischemia" does not refer to acting on the destruction of brain cells that follows cerebral ischemia, as the Majority Defendants contend; rather, it refers to acting on an imbalance of neuronal stimulation mechanisms that is cerebral ischemia (in this patent). Another problem with the Majority Defendants' proposal is that it equates "treatment" with "stopping." But the patent describes what should be done "in order to treat or eliminate this pathological situation" (JA2 at col. 2 lines 53-54) (emphasis added), indicating that "treat" is not limited to "eliminating" or "stopping" but also includes improving, alleviating, and reducing the pathological situation.

Apotex, in its proposed construction, continues to focus on blood supply, proposing: "Alleviation of an acute interruption of blood supply to the brain." Yet, as the Majority Defendants have stated, it is "very clear that this patent is not about reintroducing blood flow to the brain." (Tr. at 122) Apotex likens this case to *Rapoport v. Dement*, 254 F.3d 1053, 1056 (Fed. Cir. 2001), in which the Federal Circuit construed "treatment of sleep apnea" to mean

treatment of the underlying condition – the sleep apnea itself – and not treatment of the symptoms of sleep apnea. (D.I. 222 at 13-14; Tr. at 130-31) Here, by analogy, treatment of cerebral ischemia would require treatment of the interruption in blood supply to the brain. However, again, "cerebral ischemia" in the '703 patent relates to an "imbalance of neuronal stimulation mechanisms," not an interruption in blood supply. Thus, even assuming the reasoning of *Rapoport* applies,[8] treatment of the underlying condition of cerebral ischemia here is treatment of the imbalance of neuronal stimulation mechanisms, which supports Plaintiffs' construction.

Therefore, I recommend that "treatment of cerebral ischemia" be construed as "an antagonistic intervention with regard to the N-methyl-D-aspartate (NMDA) receptor channels."

D. "Imbalance of neuronal stimulation after Alzheimer's disease"

Plaintiffs construe this term as: "a pathophysiological situation characterized by an excessive inflow of calcium through NMDA receptor channels after Alzheimer's disease." They assert that the patentee defined the term in the following portion of the specification:

> cerebral ischemia is characterized by a pathophysiological situation defined by an imbalance of neuronal stimulation mechanisms. In this context, the excessive inflow of calcium through NMDA receptor channels finally leads to the destruction of brain cells in specific brain areas.

(D.I. 223 at 18 (citing JA2 at col. 2 lines 46-52)) Plaintiffs also point to a portion of the reexamination prosecution history, in which the patentee stated that the imbalance of neuronal stimulation that is cerebral ischemia "can be initiated by various conditions, including

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[8]As Plaintiffs note, *Rapoport* is also distinguishable because the patent there was not limited to treatment of patients with a particular diagnosis, whereas here the asserted patent claims specify that the patient must be diagnosed with Alzheimer's disease. (Tr. at 222)

Alzheimer's disease (col. 3, lines 10-16), and is characterized by a substantial increase in excitatory amino acids, which allows for an excessive influx of calcium through NMDA receptor channels leading to loss of brain cells (col. 2, lines 46-52)." (JA760-61)

Most of the Defendants, relying on the same portion of the specification cited by Plaintiffs, propose to construe the term in a manner incorporating many of the same concepts as Plaintiffs: "The destruction of brain cells, that results from an excessive influx of calcium through NMDA receptor channels (but not an imbalance of the dopamine/acetylcholine system), wherein said excessive influx is caused by an acute interruption of blood supply to the brain occurring after Alzheimer's disease."[9]

This dispute, as with others already discussed, turns on whether the focus of the patent is on an interruption of blood supply or a neuronal imbalance, and further on whether the term deals with a neuronal imbalance or on the loss of brain cells that follows it. Just as I have largely sided with Plaintiffs above, and for the same reasons, I do so here as well. The "imbalance" referred to in this term is a neuronal imbalance, not an interruption in blood supply, and not the consequences of a neuronal imbalance.

Therefore, I recommend that "imbalance of neuronal stimulation after Alzheimer's disease" be construed as "a pathophysiological situation characterized by an excessive inflow of

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[9]The Lupin and Sun Defendants propose the following construction: "A pathophysiological situation caused by cerebral ischemia occurring after Alzheimer's disease." (D.I. 222 at 27-28) Defendants Apotex and Upsher-Smith Laboratories, Inc. contend that the term need not be construed because, in their view, the claims in which it appears (claims 17 through 19) are invalid under Section 305, as these claims are impermissibly broader than original claim 1. (D.I. 222 at 23 n.15) For the reasons noted in the text, I recommend Plaintiffs' proposed construction, which is supported by the cited portion of the specification and the reexamination prosecution history. I will not address Defendants' Section 305 arguments in connection with claim construction.

calcium through the NMDA receptor channels after Alzheimer's disease."

E. "Alzheimer's disease"

Plaintiffs propose that "Alzheimer's disease" be construed as "dementia of the Alzheimer's type, as characterized by the diagnostic criteria set forth in the Diagnostic and Statistical Manual of Mental Disorders." Defendants' proposed construction is: "A progressive, neurodegenerative illness that gradually destroys a person's memory and overall cognitive ability, characterized by the presence of neurofibrillary tangles in brain cells and plaques deposited in brain tissue (also known as senile dementia of the Alzheimer's type)." Both sides agree that "Alzheimer's disease" should be construed according to its plain and ordinary meaning to one having ordinary skill in the art at the time the original patent was granted. (D.I. 223 at 3, 21 (Plaintiffs); D.I. 236 at 24-25 (Defendants))

Although the words proposed by each side differ a great deal, their proposed constructions have much in common. Two substantive points are in dispute. The first concerns whether the claim should be construed to include a reference to the "plaques and tangles" that are found in the brain of one who suffers from Alzheimer's disease. The primary way to identify such plaques and tangles in an individual's brain is through dissection, which can only be done after an individual is deceased. Since, obviously, this is not done to live patients – to whom the patent is directed – Plaintiffs insist there is no need to reference plaques and tangles in construing "Alzheimer's disease." Defendants disagree.

The record establishes that at the time the '703 patent was issued, in 1989, it was known that, post-mortem, the brain of an individual having Alzheimer's disease would contain plaques and tangles. Defendants cite to two articles demonstrating this point. *See* JA Ex. C11 at C68

(1988 article in *Medicinal Research Reviews* stating, "Postmortem microscopic examination of brain tissue [of individual who died of Alzheimer's disease] revealed high densities of lesions currently described as neuritic plaques and neurofibrillary tangles."); JA Ex. C12 at C105 (1984 article in *Neurology* stating, "The pathologic characteristics [of Alzheimer's disease] are degeneration of specific nerve cells, presence of neuritic plaques, and neurofibrillary tangles."). In connection with the reexamination, the patentees submitted a declaration of Myron Weiner, M.D., who confirmed: "It is now known that Alzheimer's disease is characterized by the presence of neurofibrillary tangles in brain cells and amyloid plaques deposited in brain tissue." (JA978) Dr. Weiner was writing in 2005, and he does not indicate when this knowledge first arose, but neither does he in any way contradict the extrinsic evidence cited by Defendants indicating it was known by 1989. Therefore, I conclude that one having ordinary skill in the art in 1989 would have understood that the plain and ordinary meaning of Alzheimer's disease included the fact that, upon dissection, the brain of one having Alzheimer's disease would be found to contain plaques and tangles.

The parties' second dispute concerns whether, among the accepted diagnostic criteria for diagnosing Alzheimer's disease in 1989, the criteria listed in the Diagnostic and Statistical Manual of Mental Disorders ("DSM") was accorded special prominence. (The then-current version of the DSM was the revised third edition, which will be referred to as "DSM-III-R.") I am persuaded that the DSM did have such a role. Plaintiffs' expert, Steven H. Ferris, Ph.D., declares: "In general, the DSM is relied upon by medical and mental health professionals . . . to arrive at a standardized diagnosis for various mental disorders. . . . The DSM is considered by healthcare professionals to be the 'dominant' reference for clinical diagnostic criteria for

dementia, including dementia of the Alzheimer's type." (D.I. 224 at ¶¶ 15-16) Defendants agree that the DSM "was *one* of the resources used in 1989 to diagnose Alzheimer's disease in patients." (D.I. 236 at 26)

Nonetheless, it is also clear that the DSM is not the only source one having ordinary skill in the art would have turned to in 1989 in determining the accepted diagnostic criteria for Alzheimer's disease. As Plaintiffs' Dr. Ferris acknowledges, "[t]he diagnostic criteria in DSM-III-R are also consistent with other well-recognized diagnostic criteria for dementia of the Alzheimer's type." (D.I. 224 at ¶ 18) He notes in particular the 1984 NINCDS-ADRDA Work Group, which promulgated clinical diagnostic criteria that "were compatible with the clinical diagnostic criteria in the DSM." (D.I. 224 at ¶ 20)

Thus, I recommend that "Alzheimer's disease" be construed as: "dementia of the Alzheimer's type, as characterized by accepted diagnostic criteria, such as those set forth in the Diagnostic and Statistical Manual of Mental Disorders, version III-R, and further characterized by the presence of neuritic plaques and neurofibrillary tangles in the brain."

F. "Patient diagnosed with Alzheimer's disease"

The parties' disagreements with respect to the claim term "patient diagnosed with Alzheimer's disease" largely rehash the disputes already discussed with respect to "Alzheimer's disease." Here, again, I believe that the accepted diagnostic criteria should single out the DSM-III-R, which would have been relied on by one having ordinary skill in the art, but should not be limited to the diagnostic criteria listed in this single reference, given the evidence that those having ordinary skill in the art would have consulted other sources as well. With respect to the "plaques and tangles" issue, because a determination of whether a patient's brain contained such

"plaques and tangles" was not part of the accepted diagnostic criteria – and, by contrast, could only be accomplished post-mortem or by a risky, inadvisable brain biopsy (D.I. 224 at ¶ 23) – there is no basis to refer to "plaques and tangles" in a term focused on diagnosis in a live patient, which is how this term is used in the patent. Accordingly, I recommend that "patient diagnosed with Alzheimer's disease" be construed as "a live patient diagnosed with dementia of the Alzheimer's type, as characterized by accepted diagnostic criteria, such as those set forth in the Diagnostic and Statistical Manual of Mental Disorders, version III-R."

G. "Treatment of an imbalance of neuronal stimulation"

The parties have not agreed on a construction of the term "treatment of an imbalance of neuronal stimulation." Their disagreements are derived from their disagreements as to the proper construction of the terms "cerebral ischemia" and "treatment of cerebral ischemia." As I have already discussed, I recommend that "cerebral ischemia" be construed as "an imbalance of neuronal stimulation mechanisms." I also recommend that "treatment of cerebral ischemia" be construed as "an antagonistic intervention with regard to the N-methyl-D-aspartate (NMDA) receptor channels." Plaintiffs propose that "treatment of an imbalance of neuronal stimulation" be construed as "an antagonistic intervention with regard to the excessive inflow of calcium through N-methyl-D-aspartate (NMDA) receptor channels."[10] I agree with Plaintiffs, as I believe this construction is properly grounded in the patent specification (*see, e.g.*, JA2 at col. 2 lines 46-

[10]The Majority Defendants propose: "Stopping the destruction of brain cells, that results from an excessive influx of calcium through NMDA receptor channels (but not an imbalance of the dopamine/aceytlcholine system), wherein said excessive influx is caused by an acute interruption of blood supply to the brain occurring after Alzheimer's disease." Defendants Lupin and Sun propose: "Treatment of a pathophysiological situation caused by cerebral ischemia occurring after Alzheimer's disease."

56) and follows from the constructions I have already recommended above.

H. "Treatment of Alzheimer's disease"

Resolution of the parties' dispute over the meaning of "treatment of Alzheimer's disease," which is found in dependent claim 10 (which depends on independent claim 1), follows from the issues I have already decided. In the context of the patent specification, one of ordinary skill in the art would agree with Plaintiffs that "treatment of Alzheimer's disease" means "treatment of cerebral ischemia after Alzheimer's disease," giving the terms "cerebral ischemia" and "Alzheimer's disease" the meanings I recommend above. By contrast, Defendants' proposed construction – "additionally for the treatment of Alzheimer's disease" – would limit claim 10 to individuals who are being treated for "cerebral ischemia" (which, according to Defendants, is the acute interruption of blood supply to the brain) and being treated for Alzheimer's disease. (D.I. 222 at 21-23; Tr. at 76, 189) This is not the proper meaning of the term, taking into account the specification as well as the relationship between claims 1 and 10. Accordingly, I recommend that "treatment of Alzheimer's disease" be construed as "treatment of cerebral ischemia after Alzheimer's disease (as those terms are defined herein)."

I. "Effective amount"

I agree with Plaintiffs that "effective amount" should be construed as "an amount shown to cause improvement, in comparison to placebo." This is the plain and ordinary meaning of the term to one having ordinary skill in the art, as is evident both from the intrinsic evidence[11] and

[11]*See, e.g.*, JA767 (patentees' reexamination filing distinguishing prior art as showing "no statistically calculable proof for the superiority of Memantine over placebo") (internal quotation marks omitted); JA970 (reexamination declaration explaining: "Physicians would have considered the results of Marcea's non-placebo-controlled study to be scientifically unreliable, both in 1989 and today. It is well established that a placebo group is a necessity in any valid drug

the extrinsic evidence.[12] Defendants' proposed construction – "an amount that is therapeutically effective" – is insufficiently precise to be helpful. Therefore, I recommend that "effective amount" be construed as "an amount shown to cause improvement, in comparison to placebo."

J. "Effective cerebral ischemia-alleviating or preventive amount"

The parties' disputes over the proper construction of "effective cerebral ischemia-alleviating or preventive amount" are derivative of their disputes over the terms "effective amount," "cerebral ischemia," and "prevention of cerebral ischemia." For the reasons I have given above in connection with the construction of these other terms, I agree with Plaintiffs here and recommend that this term be construed as: "an amount shown to treat or eliminate an imbalance of neuronal stimulation, in comparison to placebo treatment."[13]

K. "Amount effective to prevent degeneration and loss of nerve cells after ischemia"

Plaintiffs propose that this term be construed as "an amount shown to eliminate degeneration and loss of nerve cells after an imbalance of neuronal stimulation." Defendants propose instead: "An amount that is therapeutically effective to prevent degeneration and loss of

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assessment study because it enables the investigators to distinguish the effects of an experimental treatment from the effects of having no treatment at all. It was, and continues to be, an accepted standard that the experimental treatment must produce better results than the placebo in order to be considered effective."); JA981 (declaration in support of patentee during reexamination noting declarant "personally worked on a study of this drug in Alzheimer's disease patients and found that hydergine was no more effective than placebo").

[12]*See, e.g.*, JA Exs. B26-B30 (secondary sources available in 1989 explaining required process of comparing results of "experimental group" to those of placebo "control group" to determine effectiveness of proposed treatment).

[13]The Majority Defendants propose: "An amount that is therapeutically effective to prevent or stop the destruction of brain cells that results from an acute interruption of blood supply to the brain." Apotex proposes: "An amount that is therapeutically effective to alleviate or prevent an acute interruption of blood supply to the brain."

nerve cells after cerebral ischemia." I do not agree with either side. The problem with Plaintiffs' proposal is that it equates "ischemia" with "cerebral ischemia." For reasons I have earlier explained, I believe the patent uses these terms quite differently: "cerebral ischemia" is a defined term meaning "an imbalance of neuronal stimulation mechanisms" while "ischemia" is used in its plain and ordinary meaning as an "acute interruption of blood supply." Although, in context, it does not seem to make much sense that claim 13 (where this term appears) – which is dependent on claims 1 and 11, both of which relate to "cerebral ischemia" – relates to "ischemia" as opposed to "cerebral ischemia" (as I recommend that term be construed) – I cannot ignore the fact that the patentee in claim 13 chose to say "ischemia" and not "cerebral ischemia." Therefore, I recommend that "amount effective to prevent degeneration and loss of nerve cells after ischemia" be construed as "an amount shown to eliminate degeneration and loss of nerve cells after an acute interruption of blood supply."

L. "Patient in need thereof" and "patient in need of such treatment"

Plaintiffs argue that these last two "patient" terms do not require construction as they are unambiguous and should be construed according to their plain and ordinary meaning. Defendants, on the other hand, propose these constructions: "A patient in whom the need for prevention or treatment of cerebral ischemia is recognized and appreciated, and the adamantane derivative is administered with the intent of preventing or treating cerebral ischemia" (claims 1 and 14) and "A patient in which the need for treatment of imbalance of neuronal stimulation is recognized and appreciated, and the adamantane derivative is administered with the intent of treating the imbalance of neuronal stimulation" (claim 17). Defendants' constructions would, improperly, require that the patient be diagnosed with and treated for cerebral ischemia (which

Defendants construe as a disorder relating to blood supply) or imbalance of neuronal stimulation, in addition to being diagnosed with and treated for Alzheimer's disease. This is not a proper construction, given that all of the independent claims (1, 14, and 17) refer to a "patient diagnosed with Alzheimer's disease," yet none refer to a "patient diagnosed with cerebral ischemia" or "a patient diagnosed with imbalance of neuronal stimulation." Thus, I agree with the Plaintiffs that "patient in need thereof" and "patient in need of such treatment" have a plain and ordinary meaning readily understood even to a lay judge and do not require any construction. *See Phillips*, 415 F.3d at 1304.

M. Comprehensive claim construction

Finally, Defendants ask that, regardless of the constructions adopted for the individual claim terms already discussed, the Court provide a "comprehensive construction that no claim of the '703 patent can be construed to cover a method of using memantine where the only proposed indication is to treat dementia in Alzheimer's patients." (D.I. 222 at 36) Defendants assert that "the patentees affirmatively and unambiguously argued that their claims were patentable because they were limited to using memantine either for the treatment of 'cerebral ischemia' or for the treatment of 'an imbalance of neuronal stimulation.'" (D.I. 222 at 37) According to Defendants, Plaintiffs had to make such a representation to overcome the rejection over a prior art reference (Fleischhacker) they had received from the PTO. *See* JA746.

A party seeking to show a prosecution disclaimer must demonstrate an "unambiguous" disclaimer, based on "clear and unmistakable evidence" that some of the scope that would otherwise be captured by the claim was relinquished during prosecution. *See Voda v. Cordis Corp.*, 536 F.3d 1311, 1321 (Fed. Cir. 2008). Here, the prosecution history does not contain the

express disclaimer Defendants insist it does. Nowhere did the patentees unambiguously, clearly, or unmistakably disclaim the use of memantine to treat dementia of the Alzheimer's type.

The document on which Defendants rely is part of the intrinsic record created during the reexamination. It is dated May 9, 2005 and was filed by the patentee in response to the PTO's March 10, 2005 office action rejecting the reexamination claims. (JA743-47, JA751-69) That rejection was based in part on what the PTO found to be anticipation of the claims by a 1986 article by Fleischhacker. (JA746)

In response to the rejection, the patentee proposed amendments to its claims. Defendants' argument relies on a single sentence in which the patentee described its "New Claims 14-25." (JA767-68) The patentee wrote:

> Furthermore, not one of the Rote Liste, Marcea, Ambrozi, or Fleischhacker publications discloses or suggests the treatment of "cerebral ischemia" (claims 14-16), the treatment of an "imbalance of neuronal stimulation after Alzheimer's disease" (claims 17-19), "blocking an excessive influx of calcium through NMDA receptor channels" (claims 20-22), or "blocking the NMDA receptor" (claims 23-25), as called for in the present claims.

(JA768) Plainly, nothing about this sentence expressly disclaims use of memantine to treat dementia of the Alzheimer's type. Instead, it states that none of the prior art, including Fleischhacker, anticipates all of the elements of the patent's amended claims. In pointing out what is missing in the prior art – including any reference to treatment of "cerebral ischemia" or "imbalance of neuronal stimulation after Alzheimer's disease" – the patentee was neither stating nor suggesting that its own amended claims would not cover treatment of dementia of the Alzheimer's type. *See* D.I. 235 at 35 (Plaintiffs stating, "arguing that the ***prior art*** does not disclose the '***treatment*** of "cerebral ischemia"' is vastly different from arguing that the ***claims***

require a diagnosis of 'cerebral ischemia'").[14]

This conclusion is bolstered by the patentee's extended discussion of the Fleischhacker reference in a subsequent section of the same document on which Defendants rely. In a section devoted entirely to "Fleischhacker," the patentee wrote:

> Amended claim 1 and new claims 14-21 recite oral administration of the claimed compounds. Fleischhacker discloses only intravenous administration, and does not disclose or suggest any alternative routes of administration.
>
> . . . Fleischhacker expressly states that the "study showed no statistically calculable proof for the superiority of Memantine over placebo in patients suffering from SDAT [severe dementia of the Alzheimer's type]." . . . . [T]here is no disclosure in Fleischhacker that teaches or suggests that any beneficial effects of memantine have been demonstrated in Alzheimer's disease patients. Rather, that was the objective of the Fleischhacker study - an objective that was not met. Thus, if anything, Fleischhacker teaches away from the use of memantine for treating patients diagnosed with Alzheimer's disease.

(JA766-67) (internal citation omitted) It is here that the patentee expressly distinguished Fleischhacker, and did so on grounds other than that being argued by Defendants. Moreover, here, as in the portion of the document on which Defendants rely, there is neither a statement nor suggestion that the patentee is distinguishing Fleischhacker by characterizing Fleischhacker as teaching the use of memantine to treat Alzheimer's while disclaiming that use of memantine from the patent claims. Contrary to Defendants' argument, a competitor reviewing this prosecution history would not reasonably believe that the patentee had surrendered any construction which would allow the '703 patent to cover the use of memantine where the only proposed indication was the administration of memantine to treat dementia of the Alzheimer's

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[14]The PTO subsequently withdrew its March 10, 2005 rejection (made under 35 U.S.C. § 102 (anticipation)) "since the prior art does not actually teach any of the adamantane derivatives to treat cerebral ischemia and Alzheimer's disease together." (JA992)

type. (D.I. 222 at 39 (citing *PODS, Inc. v. Porta Stor, Inc.*, 484 F.3d 1359, 1368 (Fed. Cir. 2007), *cert. denied*, 128 S. Ct. 618 (2007))[15]

Therefore, I recommend that the Court reject Defendants' requested comprehensive claim construction.

RECOMMENDED CONSTRUCTIONS

For the reasons set forth above, I recommend that the Court construe the disputed terms of the '703 patent as follows:

1. "Cerebral ischemia" as that term is used in claims 1 and 14 means "an imbalance of neuronal stimulation mechanisms."

2. "Prevention of cerebral ischemia" as that term is used in claim 1 means "prevention of an imbalance of neuronal stimulation mechanisms."

3. "Treatment of cerebral ischemia" as that term is used in claims 1 and 14 means "an antagonistic intervention with regard to the N-methyl-D-aspartate (NMDA) receptor channels."

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[15]Defendants' other proffered support for their comprehensive claim construction is also unpersuasive. *See* JA633-34 (request for reexamination noting that "substantial new question of patentability may be deemed to exist" because, among other reasons, Fleischhacker was not considered during original prosecution of '703 patent, but also noting that several of original patent claims "encompass the administration of adamantane derivatives for the treatment of cerebral ischemia and the administration of memantine for the treatment of Alzheimer's disease"); JA746 (March 10, 2005 Reexamination Office Action – which was withdrawn by PTO on August 9, 2005 (JA990-92) – stating that Fleischhacker "teach[es] the administration of memantine to patients diagnosed with senile dementia of the Alzheimer's disease" and "states memantine has a beneficial effect" in such patients with respect to "increased drive and awakeness"); JA975 (declaration of Howard Fillit, M.D., filed in connection with reexamination, stating "by 1989, the only publication that expressly described the administration of memantine to Alzheimer's disease patients was Fleischhacker, and this article expressly concludes that memantine is not effective for the treatment of Alzheimer's disease").

4. "Imbalance of neuronal stimulation after Alzheimer's disease" as that term is used in claim 17 means "a pathophysiological situation characterized by an excessive inflow of calcium through the NMDA receptor channels after Alzheimer's disease."

5. "Alzheimer's disease" as that term is used in claims 1, 10, 14, and 17 means "dementia of the Alzheimer's type, as characterized by accepted diagnostic criteria, such as those set forth in the Diagnostic and Statistical Manual of Mental Disorders, version III-R, and further characterized by the presence of neuritic plaques and neurofibrillary tangles in the brain."

6. "Patient diagnosed with Alzheimer's disease" as that term is used in claims 1, 14, and 17 means "a live patient diagnosed with dementia of the Alzheimer's type, as characterized by accepted diagnostic criteria, such as those set forth in the Diagnostic and Statistical Manual of Mental Disorders, version III-R."

7. "Treatment of imbalance of neuronal stimulation after Alzheimer's disease" as that term is used in claim 17 means "an antagonistic intervention with regard to the excessive inflow of calcium through N-methyl-D-aspartate (NMDA) receptor channels."

8. "Treatment of Alzheimer's disease" as that term is used in claim 10 means "treatment of cerebral ischemia after Alzheimer's disease (as those terms are defined herein)."

9. "Effective amount" as that term is used in claims 1, 14, and 17 means "an amount shown to cause improvement, in comparison to placebo."

10. "Effective cerebral ischemia-alleviating or preventive amount" as that term is used in claim 11 means "an amount shown to treat or eliminate an imbalance of neuronal stimulation, in comparison to placebo treatment."

11. "Amount effective to prevent degeneration and loss of nerve cells after ischemia"

as that term is used in claim 13 means "an amount shown to eliminate degeneration and loss of nerve cells after an acute interruption of blood supply."

This Report and Recommendation is filed pursuant to 28 U.S.C. § 636(b)(1)(B), Fed. R. Civ. P. 72(b)(1), and D. Del. LR 72.1. The parties may serve and file specific written objections **of no longer than ten (10) pages within ten (10) days after being served with a copy of this Report and Recommendation**. Fed. R. Civ. P. 72(b). The failure of a party to object to legal conclusions may result in the loss of the right to de novo review in the district court. *See Henderson v. Carlson*, 812 F.2d 874, 878-79 (3d Cir. 1987); *Sincavage v. Barnhart*, 171 Fed. Appx. 924, 925 n.1 (3d Cir. 2006). **A party responding to objections may do so within ten (10) days after being served with a copy of objections; such response shall not exceed ten (10) pages. No further briefing shall be permitted with respect to objections without leave of the Court.**

The parties are directed to the Court's Standing Order In Non-*Pro Se* Matters For Objections Filed Under Fed. R. Civ. P. 72, dated April 7, 2008, a copy of which is available on the Court's website, www.ded.uscourts.gov/StandingOrdersMain.htm.

Dated: July 2, 2009

Honorable Leonard P. Stark
UNITED STATES MAGISTRATE JUDGE