United States District Court,
D. Delaware.

In re uc0u8242 318 PATENT INFRINGEMENT LITIGATION.

Civ. No. 05-356-SLR

Aug. 27, 2008.

Background: Exclusive licensees of patent claiming method for treatment of Alzheimer's disease with galanthamine sued generic drug manufacturers for patent infringement.

Holdings: The District Court, Sue L. Robinson, J., held that:
(1) claims of patent were not invalid due to anticipation;
(2) patent was not invalid for obviousness; and
(3) patent only surmised how the claimed method could be used, rather than teach one of skill in the art how to use the claimed method, and therefore was invalid for lack of enablement.

Judgment for defendants.

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OPINION

SUE L. ROBINSON**, District Judge.**

I. INTRODUCTION

Plaintiffs Janssen Pharmaceutica N.V. and Janssen, L.P. (collectively, "Janssen" or "plaintiffs") are the exclusive licensees of U.S. Patent No. 4,663,183 ("the '183 patent"), claiming the treatment of Alzheimer's disease with galanthamine. FN1 Janssen is the holder of approved new drug application ("NDA") No. 21-169 for galanthamine hydrobromide tablets, sold under the tradename Razadyne(R) FN2 in three dosage forms. In 2005, several generic drug manufacturers filed with the Food and Drug Administration ("FDA") abbreviated new drug applications ("ANDA's") containing paragraph IV certifications for generic galanthamine hydrobromide. *See* 21 U.S.C. s. 355(j)(2)(A)(vii)(IV). Janssen sued each for patent infringement pursuant to 35 U.S.C. s. 271(e)(2)(A).FN3 The actions were consolidated.FN4 (D.I.29) Janssen's suit triggered the 30-month stay on the FDA's approval of generic galanthamine hydrobromide.FN5 *See* 21 U.S.C. s. 355(j)(5)(B)(iii). Defendants conceded infringement of claims 1 and 4 of the '318 patent. (D.I.49) The consolidated action proceeded on three invalidity issues raised by defendants: anticipation, obviousness, and enablement. A bench trial was held between May 21, 2007 and May 25, 2007 on these issues, which were fully briefed post-trial. The court has jurisdiction pursuant to 28 U.S.C. s.s. 1331, 1338(a) and 1400(b). Having considered the documentary evidence and testimony, the court makes the following findings of fact and conclusions of law pursuant to Fed.R.Civ.P. 52(a).

FN1. Plaintiff Synaptech, Inc. is the owner of the '318 patent.

FN2. Previously labeled as Reminyl(R).

FN3. "(2) It shall be an act of infringement to submit-(A) an application under section 505(j) of the Federal Food, Drug, and Cosmetic Act or described in section 505(b)(2) of such Act for a drug claimed in a patent or the use of which is claimed in a patent[.]"

FN4. Civ. A. Nos. 05-356 (Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries Ltd.), 05-371 (Mylan Pharmaceuticals Inc. and Mylan Laboratories Inc. (collectively, "Mylan")), 05-380 (Dr. Reddy's Laboratories, Inc. and Dr. Reddy's Laboratories, Ltd.), 05-381 (Barr Laboratories, Inc. and Barr Pharmaceuticals, Inc. (collectively, "Barr")), 05-382 (Purepac Pharmaceutical Co. and Alphapharma, Inc. (collectively, "Purepac")), 05-420 (Alphapharm Pty Ltd.), 05-451 (Par Pharmaceutical, Inc. and Par Pharmaceutical Companies, Inc.). The court shall refer to these parties collectively as "defendants" in this consolidated action.

FN5. The date upon which the stay was triggered is unclear to the court. According to Janssen's complaints, the first of the ANDAs was filed with the FDA by Mylan on April 27, 2005. (Civ. No. 05-371, D.I.1) Mylan denied this allegation. (*Id.,* D.I. 12) It appears, based upon the numbering of the ANDAs, that Purepac's was actually the first ANDA filed (No. 77-585). Regardless, there is no indication of when plaintiffs received the first notice of an ANDA filing (less than or equal to 20 days after filing with the FDA), triggering the 45-day window to file suit, and whether plaintiffs initiated the first litigation (Civ. No. 03-356, filed June 3, 2005) on the 45th day or prior. *See* 31 U.S.C. s. 355(j)(2)(B); 21 C.F.R. s.s. 314.95(e) and (f). Plaintiffs represent to the court that the 30-month stay expires on August 28, 2008 by their calculation.

II. FINDINGS OF FACT AND CONCLUSIONS OF LAW

A. Background

1. Alzheimer's disease

1. In 1906, Dr. Alois Alzheimer discovered Alzheimer's disease ("AD") in a fifty-one year old female patient who had "developed memory loss and paranoia." (D.I. 384 at 95:7-17) Dr. Alzheimer performed an autopsy and observed neurofibrillary tangles and plaques, which today are the "classic ... pathological hallmarks" of AD. (*Id*.)

2. For many years, the term "Alzheimer's disease" referred to a person with "pre-senile" onset of dementia, or a person developing the condition at between 60 to 65 years of age. (*Id*. at 95:22-25) In contrast, senile dementia "refer[red] to a person who developed memory loss and dementia and appeared to have the equivalent of [AD]" with an onset age of over 60 or 65 years of age. (*Id*. at 96:14-24) By the mid-1980s, AD generally referred to "the entire spectrum of the disorder" includingboth pre-senile and senile dementia. (*Id*. at 96:6-8, 97:1-3)

3. In 1984, AD was recognized as a progressive dementia that begins with an onset of memory problems. (PTX-752 at 4924-25) As AD progresses, initial memory problems develop into more serious memory problems and begin to affect other higher brain functions, such as judgment, reasoning, language ability, perception, and recognition. (D.I. 384 at 100:4-101:4) The behavioral and functional abilities of AD patients are also affected. (*Id*.)

4. The course of AD varies broadly with each patient. For some patients, the disease can progress rapidly, within one or two years, while in others the disease can progress over a 20-year period. (*Id*.)

2. The prior art

a. Cholinergic deficit hypothesis and the focus on AChe inhibitors

5. Very little was known about the possible causes of AD until the 1970s when researchers associated decreases in acetylcholine ("ACh") FN6 levels in the brain with the disease. (D.I. 384 at 118:16-24) Specifically, researchers learned that ACh plays an important role in memory. (*Id*. at 117:24-25) Research groups determined that the chemical marker for ACh was markedly decreased in AD patients and that the extent of this decrease correlated with the number of plaques and tangles in the brain, as well as with the degree of intellectual impairment. (DTX-167 at 8268; DTX-139 at 789; D.I. 384 at 122:2-11, 124:14-126:8) This development was inspired, in part, by Dr. David Drachman's 1974 article entitled "Human Memory and the Cholinergic System." (D.I. 384 at 110:7-25, 118:4-11, 122:12-18; DTX-495)

FN6. ACh, a chemical compound, is a neurotransmitter in the peripheral and central nervous systems.

6. In the years following, several competing hypotheses existed for treating AD. (D.I. 386 at 1121:6-

1122:10) Included within these hypotheses was the "cholinergic deficit hypothesis," also referred to as the "cholinergic hypothesis." (*Id*.) The cholinergic hypothesis relates to the idea that a reduction in ACh or a deficiency in the cholinergic cells (the group of brain cells that use ACh as a chemical messenger) contributes to AD. (D.I. 384 at 126:24-128:7) Put another way, ACh reduction contributes to the clinical symptoms of AD. (*Id.;* DTX-167 at 1459)

7. By the mid-1980s, the "primary emphasis in the treatment of [AD was] on enhancing cholinergic function." (PTX-752 at 4924 (1984)) Dr. Allen Levey, Chairman of the Department of Neurology and Director of the Alzheimer's Disease Research Center at Emory University, testified for defendants that the focus in the art at that time was on enhancing cholinergic activity. (D.I. 384 at 167:11-19) Dr. Levey further explained that this was due to the "solid scientific support" the cholinergic hypothesis had received. (*Id*.) For example, a loss of cholinergic neurons was observed in the brains of AD patients autopsied after death. (PTX-663 at 1184-85)

8. Scientists developed different treatment approaches based on the cholinergic hypothesis that focused on correcting the ACh deficit: (1) pre-synaptic, (2) intra-synaptic, and (3) post-synaptic. These approaches took many forms, including ACh precursors (a pre-synaptic approach) and muscarinic agonists FN7 (a post-synaptic approach). (D.I. 384 at 128:13-130:18)

FN7. Generally, an agonist is a type of drug that binds to and alters the activity of a receptor.

9. Dr. Raymond Bartus, a leading researcher on memory loss, published an article in Science magazine in 1982 entitled "The Cholinergic Hypothesis of Geriatric Memory Dysfunction" (hereinafter, "Bartus"). (PTX-653) Under the heading "Directions for Future Research," Bartus stated:

A question that is beginning to emerge is why different cholinomimetics [FN8] seem to produce different results on memory in geriatric subjects. The absence of clear positive effects of choline and lecithin on geriatric patients is also perplexing. Among the many possible explanations, one that is consistent with all available data[,] is that the more directly one stimulates the muscarinic receptor, the more robust and consistent are the effects on memory performance in aged subjects[.]

FN8. Generally, a drug used for its actions on cholinergic systems. (D.I. 384 at 266:16-23)

(*Id*. at 1784) The direct-acting muscarinic agonists suggested by Bartus are a post-synaptic approach.

10. In 1986, D.F. Swaab and E. Fliers, of the Netherlands Institute for Brain Research, published a book chapter FN9 entitled "Clinical Strategies in the Treatment of Alzheimer's Disease" (hereinafter, "Swaab and Fliers"). (PTX-714) With respect to the cholinergic system, Swaab and Fliers noted that, "although 'some clinical improvement can occasionally be seen' (Barbeau, 1978), a satisfactory treatment of the cognitive impairment of [AD] by means of pharmacological substitution for deficits in the cholinergic system seems, at present, not to be feasible." (*Id*. at 419)

FN9. The book was entitled "Progress in Brain Research."

11. Dr. Levey testified that by 1986, the pre- and post-synaptic approaches had proved largely unsuccessful in treating AD. (D.I. 384 at 129:19-130:10) Consequently, Dr. Levey testified that one of the prominent approaches for finding a treatment for AD was the intra-synaptic approach. (*Id*. at 130:19-23) The intra-synaptic approach used drugs to block acetylcholinesterase ("AChe") activity. (*Id*.) AChe breaks down ACh in the brain, causing a deficiency of ACh in AD patients. (DTX-167 at 8268; DTX-139; D.I. 384 at 105:8-21) Cholinesterase inhibitors ("CIs") are a class of drugs which are able to inactivate AChe. (D.I. 384 at 107:13-21) By inactivating AChe, CIs raise the level of ACh by preventing it from being broken down as quickly. (*Id*.) Scientists used CIs in an attempt to increase ACh function and thereby improve cognitive function in AD patients. (*Id*. at 130:16-18; PTX-763 at 12332)

12. A tertiary amine is a compound that can cross the blood-brain barrier. (D.I. 384 at 178:5-25) As of 1986, two reversible tertiary amines, physostigmine and tetrahydroaminoacridine ("THA"),FN10 had been studied as potential treatments for AD. (D.I. 384 at 230:6-15; PX-698 at 749) Physostigmine and THA were known as reversible tertiary CIs, meaning they could enter the brain, inhibit AChe, and increase the levels of ACh in the brains of AD patients. (D.I. 384 at 178:5-179:2; D.I. 385 at 382:9-383:15) The benefits in the memory and cognitive function of AD patients attributable to these CIs were well-documented. (PTX-711 at 15615 ("THA, a centrally acting [CI], was given intravenously in varying doses to 12 unselected cases of Alzheimer-like senile dementia. Significant improvement in memory testing occurred in 6 of 12 subjects[.]") (1980); PTX-763 at 12333 ("All patients had their best performance in ability to store information in long-term memory on some dose of physostigmine rather than on the placebo saline infusion.") (1982); PTX-1205 at 27782 ("Administration of parenteral physostigmine ... has been reported to improve memory in patients with [AD] [.]") (1983); PTX-699 at 414 ("[P]hysostigmine appears to be the most viable candidate for clinical trials at present.") (1985); PTX-698 at 12997 ("Intravenous physostigmine significantly and reliably enhanced memory in 13 of 16 patients tested ... The extent of improvement was correlated with the increase in mean Cortisol secretion produced by physostigmine, suggesting that the drug improved behavior and cognition only to the extent that it had a specific central cholinomimetic effect." FN11) (1985))

FN10. Tradename, Tacrine(R).

FN11. This article also noted that "[t]wo studies with the longer acting [CI] THA have been considered in patients with advanced cases of [AD]. Modest global improvement was reported following THA administration in both studies." (PTX-698 at 12304)

13. While physostigmine and THA were shown to be effective agents for improving cognitive function in AD patients, each had reported disadvantages. A 1984 article by Kaye L. Rathmann et al. entitled "Alzheimer's Disease: Clinical Features, Pathogenesis, and Treatment" (hereinafter "Rathmann") noted that physostigmine's clinical usefulness was "limited," due to "peripheral side effects and its short duration of action." (PTX-752 at 4924) Rathmann also stated that

[n]egative findings with physostigmine have been reported; however, these studies did not individualize the dose of physostigmine. Clearly, controlled studies evaluating the long-term treatment are required to determine the clinical usefulness of [AChe] inhibitors in [AD] and to determine if the addition of an [ACh] precursor can produce greater improvement in memory than physostigmine alone. Presently, physostigmine has limited usefulness due to its very short duration of action (< 1 h[our]) and the high incidence of peripheral cholinergic side effects. However, it has served as a useful pharmacological model.

(*Id*. at 4928)

14. In 1983, THA was reported to be longer-acting, but still in the early experimental stages. (PTX-727 at 258 ("THA ... has a longer life than oral physostigmine and has few peripheral side effects (Albert & Glendhill 1945), making it an attractive pharmacologic agent. THA has not yet been extensively tested in SDAT[FN12] patients[.]"); PTX-1148 at 28273 (describing THA as "longer-acting" vis-a-vis physostigmine which "has produced global improvements in AD patients"))

FN12. Senile Dementia [of the] Alzheimer's Type.

15. These findings that physostigmine and THA improved cognitive function in AD patients increased interest in further research regarding tertiary amine CIs. (PTX-727 at 193 ("[T]rials of pharmacologic agents that enhance cholinergic activity should be aggressively pursued, as they offer a rational treatment strategy based on observed neurochemical deficits.") (1983); PTX-631 at 303 ("Recently, reports of success with [ACh] inhibitors, such as physostigmine, have aroused considerable interest[.]") (1984); PTX-632 at 343 ("[T]he available studies with cholinergic agents provide the optimist with a basis of hope for future drug development, but they admittedly offer no immediate promises of providing effective therapeutic intervention.") (1985))

16. Notwithstanding, as of 1985, the medical community did not perceive any drugs to be viable treatments for AD; none, in fact, were approved by the FDA. (D.I. 386 at 1079:4-1080:21; PTX-213 at 307 ("Despite sporadic reports of barely detectable improvements with various drugs or drug combinations, therapeutic efforts have, in general, failed to produce improvement of clinical value.") (1985))

17. According to Dr. Levey, the field in 1986 was focused on muscarinic receptors, as the "preponderance of the evidence was that muscarinic receptors were the class that was most important for the symptomology of [AD.]" (D.I. 384 at 259:4-11) From about 1985 onwards, Dr. Levey himself had "specifically focused on the muscarinic acetylcholine receptors since they are the primary targets of any cholinergic replacement therapies." (*Id*. at 303:6-7; PTX-1223)

b. Galanthamine prior art

18. Galanthamine is a reversible tertiary CI in the same class as physostigmine and THA. (DTX-71)

19. In 1961, K.G. Pernov published an article in the Psychiatry Neurology and Medical Psychology journal entitled "Nivalin[FN13] and its Curative Effect upon Diseases of the Nervous System" (hereinafter, "Pernov"). (PTX-1181) Pernov characterized galanthamine hydrobromide as a "new, more powerful cholinesterase inhibitor." (*Id*. at 5983) The abstract provides:

FN13. "Nivalin" is synonymous with galanthamine. (D.I. 384 at 202:5-7)

Nivalin (galanthamin) is a new drug, inhibiting cholinesterase with a wide field of action. It is a tertiary amine, resembling eserine[FN14], but is much less toxic. It is distinguished from prostigmin, which is a quaternary amine, chiefly by the duration of its action.

FN14. "Eserine" is synonymous with physostigmine. (D.I. 384 at 179:7-8)

Nivalin has a very good curative effect upon diseases of the neuromuscular apparatus-myasthenia gravis pseudoparalytica, dystrophia musculorum progressiva, etc.-and upon lesions of the peripheral motoric neuron, the residual stage of poliomyelitis, neuritis (above all neutitis n. facialis), polyneuritis, etc. In many cases also a good influence upon lesions of the central motoric neuron was observed, such as cerebral poliomyelitis, multiple sclerosis, [etc.] ...
Nivalin is applied subcutaneously in doses increasing up to 10-25 mg per day. The drug is very well tolerated, side effects are rare.

(*Id*. at 5988)
20. There are two types of cholinergic receptors. Muscarinic receptors are membrane-bound ACh receptors that are more sensitive to muscarine than to nicotine. Those ACh receptors for which the opposite is true are known as nicotinic receptors. Myasthenia gravis, as discussed by Pernov, is a condition affected by nicotinic receptors. The central motor neurons are "largely muscarinic" receptors. (D.I. 384 at 263:20-24) CIs do not act on the nicotinic or muscarinic receptors-they simply inhibit AChe, thus preserving ACh. (PTX-752 at 4928)

21. In 1969, Dr. A.R. Luria et al. from the Moscow University and N.N. Burdenko from the Neurosurgical Institute in Moscow published a chapter in The Handbook of Clinical Neurology entitled "Restoration of higher cortical function following local brain damage" (hereinafter, "Luria"). Luria stated that galanthamine, "the strongest known [CI]," is "tolerated better" than physostigmine and "possesses a more marked and lasting effect." (PTX-744 at 5975)

22. In 1971, Dr. D.A. Cozanitis and Dr. E. Toivakka, anesthesiologists with the Third Surgical Clinic and Clinic of Neurosurgery of Helsinki University Central Hospital of Jelinski, Finland, published an article entitled "A Comparative Study of Galanthamine Hydrobromide and Atropine/Neostigmine in Conscious Volunteers," in which the authors characterized galanthamine as having "central action" and "very slight muscarinic effect." (PTX-1339 at 12342)

23. In January 1974, Dr. P.A. Bhasker published an article in "The Antiseptic," a monthly journal of medicine and surgery published in India, entitled "Medical Management of Dementia" (hereinafter, "Bhasker"). (DTX-483) Bhasker stated that, "[w]ith regard to progressive dementia, there appears very little to offer. Only management and no treatment is possible." (*Id*. at 12374) Bhasker also provided the following:

The restoration of higher cortical functions is difficult and was once considered to [be] impossible, but it has lately gained importance. Luria and his colleagues have dealt with this problem in great detail. They have suggested measures of improving the higher functions in cases of local brain damage like tumour, head injury, infarct etc., by deinhibitory procedures and re-education of the rest of the brain. Deinhibition refers to the facilitation of [ACh] activity by giving small daily doses of cholinesterase inhibitors (neostigmine, **galanthamine** etc.).

(*Id*. at 12375) (emphasis added)

24. As early as 1974, scientists appreciated that the administration of scopolamine, a selective blocker of

muscarinic receptors, mimicked the memory loss of old age. (PTX-632 at 338 & n. 34) By 1982, these age mimicking effects "were shown to be at least somewhat specific to its effects on central muscarinic receptors, since similar age-like effects on memory were not obtained with a number of other drug treatments, including ... nicotinic receptor blockers." (*Id*. at 338 & n. 43)

25. A 1977 article by Dr. Cozanitis, entitled "Galanthamine Hydrobromide, a Longer Acting Anticholinesterase Drug, in the Treatment of the Central Effects of Scopolamine (Hyoscine)" (hereinafter, "Cozanitis"), disclosed that galanthamine hydrobromide has "certain advantages over physostigmine" in treating the central effects of scopolamine. (DTX-70 at 649) Specifically, Cozanitis disclosed that galanthamine hydrobromide is "long acting," and "was used successfully in a patient having taken a large dose of dextromoramide," a powerful opioid analgesic. (*Id*. at 650) Cozanitis stated that "galanthamine hydrobromide might be very advantageous in anaesthesia when a patient has been given scopolamine for pre-medication prior to the use of a non-depolarizing relaxant[.]" (*Id*.) Further, "[s]tudies of the dose of galanthamine hydrobromide needed for treatment of patients showing the manifestations of scopolamine and related drug toxicity are indicated[,]" though a 20 mg dose was used in the case reported. (*Id*.)

26. In 1977, Dr. Anis Baraka et al. published an article that appeared in the Journal of the American Medical Association entitled "Reversal of Central Anticholinergic Syndrome by Galanthamine" (hereinafter, "Baraka"). (DTX-71) Baraka disclosed the use of a galanthamine hydrobromide injection FN15 in multiple patients, resulting in the "effective[ ] revers[al of] the central anticholinergic syndrome caused by scopolamine overdosage." Baraka noted that "[s]copolamine and related anticholinergic compounds that cross the blood-brain barrier can result in the central anticholinergic syndrome characterized by drowsiness, disorientation, delusions, and hallucinations." Baraka stated that "[e]vidently, galanthamine as well as physostigmine can inhibit brain [ACh] activity and produce marked EEG [FN16] activation." Galanthamine was characterized as superior to physostigmine, insofar as it did not suffer from "relatively short duration of action" because it is "hydrolysis-resistant," decreasing hydrolytic cleavage of the compound in the body. (*Id*.)

FN15. The copy of DTX-71 admitted to the record is barely legible. The dose of the injection used cannot be discerned.

FN16. Electroencephalography, or generally, the measurement of electrical activity produced by the brain via electrodes placed on the scalp.

27. In 1980, D. Daskalov et al. published an article entitled "Nivalin: Application in Rehabilitation Treatment of Cerebral Diseases with Aphasic Syndromes" (hereinafter, "Daskalov"). (PTX-743) Daskalov disclosed that the administration of between 3 mg and 20 mg daily of galanthamine, for a duration of between 17 to 104 days, resulted in the improvement in communicative abilities in 16 out of 23 test subjects with aphasia, or a loss in the ability to produce and/or comprehend language due to brain injury (such as a stroke). (*Id*.)

3. The invention and the '318 patent

28. Dr. Bonnie Davis is a medical doctor whose research focused on neuroendocrinology, the study of the relationship between brain function and hormonal release in the body. (D.I. 385 at 686:15-20) Through her

work, Dr. Davis developed a "neuroendocrine window," a tool that allowed her to hypothesize about the effects that cholinergic drugs had on the brain by measuring hormone levels in the blood. (*Id*. at 698:19-25)

29. Dr. Davis believed that it was very important to replace both the nicotinic and muscarinic aspects of ACh in AD patients. (D.I. 389 at 710:20-711:7) She disagreed with the focus in the field on only the muscarinic receptors, in part because she characterized AD as a disease not only of memory, but of learning-a central nicotinic effect. (*Id*. at 696:18-698:9)

30. Dr. Davis determined that the hormone Cortisol was a good marker for measuring whether ACh was active in the brain, that is, an increase in basal Cortisol levels in the blood indicates the presence of active ACh.FN17 (*Id*. at 700:1-25) Dr. Davis first realized that galanthamine would work as a treatment for AD after reading a 1974 article by Dr. Cozanitis (PTX-829), which described administering galanthamine to patients after surgery to reduce curare FN18. (D.I. 389 at 704:8-18) Dr. Cozanitis reported that galanthamine caused a sustained rise in Cortisol which lasted six hours; he believed this was a stress response.FN19 (*Id*. at 706:24-707:5) In contrast, Dr. Davis thought that the rise in Cortisol was due to "a specific central stimulation of the nicotinic pathway." (*Id*. at 709:1-710:9)

FN17. More specifically, the adrenal cortex (the outside part of the adrenal gland on top of the kidney) makes Cortisol when it is stimulated by the pituitary gland, the pituitary gland causes Cortisol secretion when it makes adrenocorticotropic hormone ("ACTH"), ACTH is made when the pituitary gland is stimulated by corticotropin releasing factor ("CRF") in the hypothalamus, and CRF is secreted when ACh operates via a nicotinic receptor. (D.I. 389 at 699:2-700:5)

FN18. Generally, the effects of a preparation of a toxic alkaloid obtained from the plant Chondrodendron tomentosum, used in surgery due to its powerful muscle relaxant properties.

FN19. Dr. Cozanitis cited the work of Dr. Naumenko, who had previously determined that galanthamine causes a rise in Cortisol in guinea pigs based upon what he believed was a stress response. (D.I. 389 at 707:6-709:9)

31. Having conceived of using galanthamine for AD, Dr. Davis sought to procure a sample of galanthamine for preclinical studies. (*Id*. at 715:13-718:15; PTX-121; PTX-122; PTX-123) Galanthamine was unavailable in the United States in 1985 and 1986. (D.I. 389 at 718:12-15) Dr. Davis was unable to obtain galanthamine prior to filing her patent application. (*Id*. at 718:16-25) Likewise, no clinical studies were performed prior to filing.

32. The '318 patent was filed as U.S. Patent Application No. 06/819,141 on January 15, 1986, naming Dr. Davis as the sole inventor. Originally-filed claim 1, the only independent claim, read:

A method of treating and diagnosing Alzheimer's disease and related dementias which comprises administering to a patient suffering from such a disease a therapeutically effective amount of galanthamine or a pharmaceutically acceptable acid addition salt thereof.

(PTX-2) The claims were rejected by the examiner on April 10, 1986 on two bases: (1) under 35 U.S.C. s.

112, second paragraph, as being indefinite in view of the term "diagnosing" in claim 1; and (2) under 35 U.S.C. s. 103, as obvious in view of two chemical abstract references noted in the specification. The first reference was an abstract of a paper published in the Journal of Highest Nervous Activity by Kraus ("the Kraus article"), and the second reference was an article by Chaplygina and llyuchenok ("the C & l article"). In traversing the rejection, Dr. Davis asserted that neither the Kraus article nor the C & l article, which indicated that galanthamine has an effect on improving short term memory and on restoring memory after it has been destroyed, renders obvious the use of galanthamine for AD for several reasons. Specifically, in addition to memory loss, AD is associated with physiological changes such as degeneration of nerve cells, damage to neural pathways and tangles: "To say that simply because a particular drug has some effect on a symptom caused by one underlying condition, it will have a useful effect on another underlying condition is clearly wrong." (PTX-14 at 3-4)

33. With respect to enablement, Dr. Davis deleted the reference to "diagnosis" from claim 1. Dr. Davis further stated that she

currently has experiments underway using animal models which are expected to show that treatment with galanthamine does result in an improvement in the condition of those suffering from [AD].

(PTX-14 at 2) Dr. Davis testified at trial that, prior to the date of her response to the examiner (September 9, 1986), a member of her research group had successfully obtained galanthamine from Russia and provided it to Dr. Joseph T. Coyle, then Director of the Division of Child Psychiatry and neuroscience professor at Johns Hopkins,FN20 for use in animal experiments. (D.I. 389 at 722:20-723:9)

FN20. Dr. Coyle is currently a professor at Harvard Medical School. He was formerly Chairman of Psychiatry between 1991 and 2001 at that institution.

34. A Notice of Allowance was mailed to Dr. Davis on October 20, 1986. The issue fee was paid shortly thereafter. On December 15, 1986, Dr. Davis mailed a letter to the examiner enclosing newly-discovered prior art "demonstrat[ing] that[,] despite the fact that galanthamine has long been available and many of its properties are well known, there has been no suggestion of its use for treatment of [AD][.]" (PTX-2) The '318 patent issued on May 5, 1987. FN21 As issued, claim 1 reads: "A method of treating Alzheimer's disease and related dementias which comprises administering to a patient suffering from such a disease a therapeutically effective amount of galanthamine or a pharmaceutically-acceptable acid addition salt thereof." (PTX-1 at col. 3, ll. 6-10) Dependent on claim 1, claim 4 reads: "A method according to claim 1, wherein said administration is oral and is in the range 10-2000 mg per day." (*Id*. at col. 4, ll. 3-5)

FN21. The term of the '318 patent was extended on October 22, 2004 pursuant to 35 U.S.C. s. 156; the '318 patent expires in December 2008.

35. Dr. Coyle had not finished the animal studies by the time the '318 patent was allowed in October 1986 or issued in May 1987. (D.I. 389 at 723:15-20) Dr. Coyle first provided Dr. Davis with his animal testing results by letter dated July 7, 1987. (PTX-831, D.I. 389 at 724:22-25) In this letter, Dr. Coyle reported that treatment with galanthamine reversed the performance deficit induced by scopolamine administration in mice, and was effective three hours after administration. (PTX-831) Dr. Coyle discussed his results in an article entitled "A Long-Acting Cholinesterase Inhibitor Reverses Spatial Memory Deficits in Mice,"

submitted to the Pharmacology Biochemistry & Behavior Journal on January 11, 1988.FN22 (PTX-117) In the abstract of his paper, Dr. Coyle stated that "[g]alanthamine's ability to reverse cognitive deficits induced by nBM[FN23] lesions and its comparatively long half-life suggest that it may be effective in treating the central cholinergic deficits in [AD] patients." (*Id.*)

FN22. The article was published at vol. 31, pp. 141-47 of that journal.

FN23. Generally, a group of nerve cells in the basal forebrain, rich in Ach and AChe.

4. Dr. Davis's licensing efforts

36. Between 1987 and 1989, Dr. Davis attempted, without success, to find a pharmaceutical company to license the '318 patent and pursue the development of galanthamine for treatment for AD. (D.I. 329 at 728:1-730:14) Several companies communicated to Dr. Davis a skepticism regarding the success of CIs in the treatment of AD.FN24

FN24. Wyeth indicated that "the potential for success of tacrine and physostigmine and other anti-cholinesterase products is not very positive." (PTX-596) Wyeth again turned Dr. Davis down after additional data were provided to Wyeth, explaining that "[t]here is still skepticism regarding the success of [CIs] in the treatment of senile dementia." (PTX-323) In 1989, Bristol-Myers Squibb indicated that "[u]nfortunately, clinical experience with galanthamine in [AD] patients is, presently, very limited. Therefore, the therapeutic benefit and long-term safety and tolerability of galanthamine is still a matter of speculation." (PTX-119)

37. As of 1989, there were no lead drugs for the treatment of AD. (D.I. 386 at 1087:1-4) At a 1989 FDA symposium to promote the development of AD treatments, Dr. Paul Leber, the director of the division of the FDA responsible for antidementia drugs, observed that "at this point in time, even a safe and effective symptomatic treatment for some cardinal sign and symptom of Alzheimer's would constitute a substantive therapeutic advance." FN25 (D.I. 386 at 1083:15-1084:1; DTX-1122 at 10:2-5)

FN25. Also expressing skepticism about the currently available drugs for AD treatment, Dr. Drachman, at the symposium, stated that "[w]e don't have any drugs that are really doing a hell of a lot." (PTX-1122 at 38:2-3; D.I. 386 at 1088:1-11)

38. In 1990, Dr. Davis successfully licensed the '318 patent to The Ciba-Geigy Chemical Corporation ("Ciba"). (PTX-305) Ciba performed animal toxicology studies and a clinical study. Despite positive results, Ciba terminated its license in 1993 due to limited resources, "without having any doubts with either the efficacy or safety of galanthamine." (D.I. 389 at 758:19-763:6; PTX-833 at 15429; PTX-467) Dr. Davis licensed the '318 patent in November 1995 to Janssen. (PTX-329) Janssen worked with Synaptech to complete the clinical studies, which were positive, and Janssen received FDA approval for galanthamine for the treatment of mild to moderate AD on February 28, 2001. (D.I. 389 at 768:4-769:12)

B. Discussion

Defendants assert that the '318 patent is invalid under three theories: anticipation (35 U.S.C. s. 102(b)); obviousness (35 U.S.C. s. 103); and lack of enablement (35 U.S.C. s. 112, second paragraph). The court first construes the disputed claim terms, and addresses defendants' invalidity arguments in turn.

1. Claim construction

The parties sought the court's assistance in defining two claim terms: (1) "Alzheimer's disease and related dementias"; and (2) "method of treating" (in the context of providing a therapeutically effective amount of galanthamine to AD patients). Having heard oral argument on, and having reviewed the papers submitted in connection with, the parties' proposed claim construction, the court construes the disputed claim language consistent with the tenets of claim construction set forth by the Unites States Court of Appeals for the Federal Circuit in Phillips v. AWH Corp., 415 F.3d 1303 (Fed.Cir.2005), as follows:

39. "**[A]nd related** dementias" includes presenile dementia of the Alzheimer's type, SDAT, and dementia associated with Down's Syndrome. There is no disagreement between the parties regarding this definition, FN26 and it is generally consistent with the testimony of record. (D.I. 384 at 318:3-14 (Dr. Levey); D.I. 323, ex. 5 at 136:6-137:17 (plaintiffs' expert Dr. Jeffrey L. Cummings))

FN26. The parties agreed that the term "Alzheimer's disease" means presenile dementia, as defined in the specification. (PTX-1 at col. 1, l. 34) The parties previously disagreed on the scope of "related dementias." "Related dementias" is not defined in the specification or prosecution history. In their claim construction papers and at oral argument, plaintiffs asserted that "related dementias" (plural) includes only SDAT. (D.I. 321; D.I. 322 at 8-10) In their post-trial papers, however, plaintiffs asserted that "related dementias" means both SDAT and Down's Syndrome, because these conditions are, like AD, characterized by plaques and tangles. (D.I. 398 at 17) Defendants agree that SDAT and Down's Syndrome should be included amongst AD's "related dementias" and, in addition, asserts that "related dementias" includes, without limitation, dementias related to Parkinson's disease, Lewy body disease, cerebral palsy, and several other conditions. (D.I. 324 at 9; D.I. 408 at 3) The court need not define (with limitation) all possible "related dementias" at this juncture.

40. "**[M]ethod of treating**": A method of alleviating the symptoms or deferring the decline associated with AD and related dementias, including the cognitive impairment that is the core symptom of such diseases.

41. It is an object of the '318 patent "to improve the cognitive function of patients with [AD][,]" not necessarily the functional status of persons with the disease. (PTX-1 at col. 1, ll. 38-42 (noting that "[a]t present, there is no effective means of improving the functional status of persons with the disease.")) That is, the invention is described as "[a] method for treating [AD] and related dementias which comprises administering to mammals, including humans, an effective [AD] **cognitively-enhancing** amount of galanthamine or a pharmaceutically-acceptable acid addition salt thereof." (*Id.*, col. 1, ll. 45-50) (emphasis added) Defendants' proposed construction, the "administration of a drug product (i.e., galanthamine) to improve the cognitive function or functional status of a patient with [AD] or related dementias," would allow the claim to mean that galanthamine can be used merely to enhance functional status without improving cognitive function-a result that is inconsistent with the intrinsic record. (D.I.321) (emphasis added)

42. AD and related dementias are characterized by a progressive decline in cognitive function. This decline

may be gradual (over 20 years) or abrupt (within one to two years). (D.I. 384 at 100:4-101:4) To improve this symptom, claim 1 provides that galanthamine may be administered to either alleviate the decline in cognitive function or to defer further decline in cognitive function-either results in an enhancement of cognitive ability as compared to the gradual decline which would take place absent the treatment.

2. Anticipation

a. Standard

[1][2] 43. A patent is anticipated under 35 U.S.C. s. 102 if a single prior art reference explicitly discloses each and every limitation of the claimed invention. *See* SmithKline Beecham Corp. v. Apotex Corp., 403 F.3d 1331, 1343 (Fed.Cir.2005). The prior art reference must be a printed publication, published more than one year prior to the date of the patent application in the United States. *See* Helifix Ltd. v. Blok-Lok, Ltd., 208 F.3d 1339, 1346 (Fed.Cir.2000). The Federal Circuit has stated that "[t]here must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention." Scripps Clinic & Research Found. v. Genentech, Inc., 927 F.2d 1565, 1576 (Fed.Cir.1991). "In determining whether a patented invention is [explicitly] anticipated, the claims are read in the context of the patent specification in which they arise and in which the invention is described." Glaverbel Societe Anonyme v. Northlake Mktg. & Supply, Inc., 45 F.3d 1550, 1554 (Fed.Cir.1995). The prosecution history and the prior art may be consulted "[i]f needed to impart clarity or avoid ambiguity" in ascertaining whether the invention is novel or was previously known in the art. Id. (internal citations omitted).

[3] 44. A prior art reference also may anticipate without explicitly disclosing a feature of the claimed invention if that missing characteristic is inherently present in the single anticipating reference. *See* Continental Can Co. USA v. Monsanto Co., 948 F.2d 1264, 1268 (Fed.Cir.1991). The Federal Circuit has explained that an inherent limitation is one that is necessarily present and not one that may be established by probabilities or possibilities. *See* id. at 1268-69. That is, " '[t]he mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " Id. at 1269 (citations omitted). The Federal Circuit also has explained that "inherency operates to anticipate entire inventions as well as single limitations within an invention." Schering Corp. v. Geneva Pharms. Inc., 339 F.3d 1373, 1380 (Fed.Cir.2003). Recognition of the inherent limitation by a person of ordinary skill in the art before the critical date is not required to establish inherent anticipation. *See* id. at 1377.

[4][5][6] 45. An anticipation inquiry involves two steps. First, the court must construe the claims of the patent in suit as a matter of law. *See* Key Pharm. v. Hercon Labs. Corp., 161 F.3d 709, 714 (Fed.Cir.1998). Second, the finder of fact must compare the construed claims against the prior art. *See* id. A finding of anticipation invalidates the patent. *See* Applied Med. Resources Corp. v. U.S. Surgical Corp., 147 F.3d 1374, 1378 (Fed.Cir.1998). Issued patents are presumed valid, and the "underlying determination of invalidity ... must be predicated on facts established by clear and convincing evidence." Rockwell Int'l Corp. v. United States, 147 F.3d 1358, 1362 (Fed.Cir.1998) (citations omitted).

b. Discussion

[7] 46. Defendants assert that the '318 patent is invalid in view of Bhasker, published in 1974, which focused on the management of dementias. Bhasker provides that the dementing process generally is a "relentlessly progressive one" and "very often not amenable even to diagnosis." (DX-483 at 12374) As Dr. Levey testified, the first several paragraphs of Bhasker discuss several types of dementias: reversible

dementia, arrested dementia, irreversible dementia, and progressive dementia. (D.I. 384 at 208:14-210:14, 212:5-213:9) Arrested dementias will neither worsen nor improve despite locating and treating the cause of the dementia. (*Id*. at 209:18-210:1, 218:14-21) Arrested dementias may be caused by a brain tumor, head injury, or stroke. (*Id*. at 209:21-22) A progressive dementia, according to Bhasker, is "a progressive fall-out of neurons and the course of the illness is rapidly downhill." FN27 (DX-483 at 12374; D.I. 384 at 211:5-10) One having ordinary skill in the art in 1974 and 1986 would have categorized AD as a progressive dementia, or a dementia that is neither arrestible or reversible with treatment. (D.I. 384 at 210:6-18, 213:2-9; D.I. 389 at 488:14-17; D.I. 386 at 990:9-991:2)

FN27. In 1974, AD typically was diagnosed very late and, therefore, the course of the dementia would occur "very rapidly." (D.I. 384 at 211:21-212:4)

47. Pursuant to the court's claim construction, "[AD] and related dementias" constitutes a subset of progressive dementias. According to Bhasker, "[w]ith regard to progressive dementia, there appears very little to offer. Only management and no treatment is possible." (DTX-483 at 12374) In paragraphs subsequent to this statement, various methods of managing dementia patients are identified, including the use of drugs to control seizures and behavioral problems. (*Id.;* D.I. 384 at 213:17-215:9) Thereafter, Bhasker does not disclose the use of galanthamine to treat AD, but does disclose the administration of "small daily doses of [CIs] (neostigmine, galanthamine etc.)" to aid the "restoration of higher cortical functions" in patients suffering from dementia caused by "local brain damage like tumour, head injury, infarct etc.," i.e., arrested dementia. (DTX-483 at 12375)

48. Dr. Levey contends that Bhasker anticipates the '318 patent because it discloses treatment of patients with progressive dementia. (D.I. 396 at 18) According to Dr. Levey, because Bhasker disclosed using CIs for restoring "higher cortical functions"-functions such as memory, which are also impacted by AD-Bhasker disclosed using galanthamine to treat progressive dementias like AD. (D.I. 384 at 186:3-14, 218:25-220:6,FN28 221:24-223:7) The court disagrees.

FN28. Defendants contend that the following testimony was either a transcription error or misstatement as evidenced by other portions of Dr. Levey's testimony: "To me, it's absolutely inherent ... that he's suggesting cholinesterase inhibitors might be tried for treating dementia, **arrested dementia.** That one might restore cortical functions, as has been shown to be the case for local brain injury." (D.I. 384 at 219:14-220:3) (emphasis added) Defendants assert that Dr. Levey meant progressive dementias. (*See id*. at 220:4-6 (question immediately following alleged [mis]statement: "And progressive dementias include [AD]; is that right?"); 222:2-223:6 ("Because as we just walked through it, [Bhasker] talked about treatment of patients with progressive dementia."); 216:17-19 ("Higher cortical functions refers to the cognitive functions that are implicated in-progressive dementia and [AD.]"); 319:21-320:3 (Bhasker describes galanthamine "as a treatment broadly for the category progressive dementia...."); 320:4-321:19 (Bhasker describes galanthamine as a potential treatment for some, but not all, progressive dementias)) Reading Dr. Levey's testimony as a whole, the court agrees that Dr. Levey likely misspoke in this instance.

49. As Dr. Levey testified, and as noted in Bhasker, progressive dementias and arrested dementias are not identical conditions. Arrested dementias "cause problems with higher cortical functions, but they don't get progressively worse" (*id*. at 218:20-21), while progressive dementias implicate degenerative changes. (*Id*. at 213:1) The fact that the two types of dementias have common symptoms (e.g., loss in higher cortical

functions such as memory) does not change this fact. Because the conditions differ, Bhasker's disclosure of the use of galanthamine for one condition does not necessarily equate to a disclosure of the use of galanthamine to treat the other. Bhasker stated that "no treatment is possible" for progressive dementia. (DTX-483 at 12374) Another of defendants' witnesses, Dr. Edward Domino, an Active Emeritus Professor of Pharmacology at the University of Michigan, testified that the reference in Bhasker to dementias caused by localized injury did not refer to AD. (D.I. 389 at 488:10-17) In view of the foregoing, the court finds that defendants have not demonstrated, by clear and convincing evidence, that Bhasker discloses the use of galanthamine to treat AD or related dementias as defined by the court; claims 1 and 4 are not invalid due to anticipation.

3. Obviousness

a. Standard

[8] 50. "A patent may not be obtained ... if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. s. 103(a). Obviousness is a question of law, which depends on several underlying factual inquiries.

Under s. 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.

KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 127 S.Ct. 1727, 1734, 167 L.Ed.2d 705 (2007) (quoting Graham v. John Deere Co., 383 U.S. 1, 17-18, 86 S.Ct. 684, 15 L.Ed.2d 545 (1966)). "Because patents are presumed to be valid, *see* 35 U.S.C. s. 282, an alleged infringer seeking to invalidate a patent on obviousness grounds must establish its obviousness by facts supported by clear and convincing evidence." Kao Corp. v. Unilever U.S., Inc., 441 F.3d 963, 968 (Fed.Cir.2006) (citation omitted).

[9] 51. "[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." KSR, 127 S.Ct. at 1741. Likewise, a defendant asserting obviousness in view of a combination of references has the burden to show, by clear and convincing evidence, that a person of ordinary skill in the relevant field had a reason to combine the elements in the manner claimed. Id. at 1741-42. The Supreme Court has emphasized the need for courts to value "common sense" over "rigid preventative rules" in determining whether a motivation to combine existed. Id. at 1742-43. "[A]ny need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." Id. at 1742.

[10] 52. In addition to showing that a person of ordinary skill in the art would have had reason to attempt to make the composition or device, or carry out the claimed process, defendants must also demonstrate, by clear and convincing evidence, that "such a person would have had a reasonable expectation of success in doing so." PharmaStem Therapeutics, Inc. v. ViaCell, Inc., 491 F.3d 1342, 1360 (Fed.Cir.2007).

b. Parties' arguments

[11] 53. According to defendants, Bhasker, alone or in combination with a variety of prior art references, disclosed all of the limitations of claim 1 of the '318 patent. (D.I. 396 at 25) With respect to a motivation to combine, defendants assert that galanthamine would have been "obvious to try" for AD, insofar as there were a "finite number of identified, predictable solutions" for treating AD in 1986, and galanthamine's central cholinergic effects were well-known. (D.I. 396 at 26, citing KSR, 127 S.Ct. at 1742) Defendants also claim that a person of ordinary skill in the art would have used the intra-synaptic approach, and would have thereafter been led "directly" to galanthamine, for two reasons: success in improving cognitive function had been reported with the use of physostigmine and THA, compounds in the same class; and the prior art disclosed that galanthamine had a better side effect profile and longer duration of action. Plaintiffs assert that, in 1986, galanthamine was known as "a weak and short acting [CI] with predominantly peripheral, nicotinic effects"-exactly the opposite of what the AD field was looking for in 1986. (D.I. 398 at 36)

54. In KSR, the Supreme Court stated that "the fact that a combination was obvious to try might show that it was obvious under s. 103" in certain circumstances. 127 S.Ct. at 1742. That is,

[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

Id. Defendants assert that there were indeed "a finite number of identified, predictable solutions" to improve cognitive function in AD patients, and Dr. Davis did nothing more than substitute one reversible tertiary amine CI with proven capabilities (galanthamine) for another (physostigmine or THA) to achieve this purpose.

55. Defendants' "obvious to try" argument has two premises: first, that a person of ordinary skill in the art FN29 would have followed the intra-synaptic approach, insofar as it was the only approach with "proof of concept" FN30 in 1986; and second, that such a person would have been led "directly" to galanthamine, a reversible tertiary amine CI like physostigmine and THA, because the prior art disclosed that galanthamine had a better side effect profile and longer duration of action.

FN29. The court notes at this juncture that the parties do not dispute a "person of ordinary skill in the art" with respect to the '318 patent is an M.D. or Ph.D. with knowledge and training in the pathology and treatment of AD, also having knowledge of pharmacology. (D.I. 396 at 23; D.I. 398)

FN30. Proof of concept means that experimental evidence exists to support the hypothesis. (D.I. 384 at 164:17-18)

c. Numerosity of viable approaches

56. As an initial matter, the court disagrees with defendants' assertion that a person of ordinary skill in the art looking to decrease ACh loss in AD patients (or reduce its effects) would have been more likely to approach the problem using the intra-synaptic approach than another alternative.

57. Defendants support their argument with the testimony of Dr. Levey, who indicated that, as of 1986,

scientists had not achieved significant success with either the pre-synaptic or post-synaptic approaches. (D.I. 384 at 129:10-130:10) FN31 In contrast, there was proof of concept to support using CIs to treat AD. (*Id*. at 164:19-21) As discussed previously, persons of skill in the art were achieving some degree of success with the intra-synaptic approach (physostigmine and THA) at that time. (PTX-727 at 193 ("[T]rials of pharmacologic agents that enhance cholinergic activity should be aggressively pursued, as they offer a rational treatment strategy based on observed neurochemical deficits.") (1983); PTX-631 at 303 ("Recently, reports of success with [AChe] inhibitors, such as physostigmine, have aroused considerable interest[.]") (1984))

FN31. Dr. Levey summarily testified that the pre-synaptic and post-synaptic approaches did not have success as of 1986. Defendants also assert that Bartus indicates that "it was questionable whether the post-synaptic approach would treat AD" (D.I. 396 at 26); the court reads Bartus to disclose some skepticism regarding all of the treatments available as of 1985. (PTX-632 at 343) Defendants point to no testimony in support of their interpretation or to the contrary.

58. Commensurately, however, both Bartus (in 1982) and Johns (in 1983) identified the post-synaptic approach as the most promising. (PTX-653 at 1784 (suggesting that direct stimulation of the muscarinic receptor, a post-synaptic approach, would result in "more robust and consistent" effects on memory performance); PTX-727 at 192 (disclosing that administering cholinergic agents which work directly at post-synaptic receptor sites had potential for treating AD)) In 1983, Dr. Domino, defendants' expert, was using a pre-synaptic approach. Dr. Domino used the ACh precursor lecithin along with a metabolic enhancer (Hydergine(R)), and found some subjective improvements in patient functionality with the use of Hydergine(R). (DTX-557; D.I. 389 at 466:16-471:5) Professor L.E. Hollister of Stanford University characterized "ergoloid mesylates of piracetam," metabolic enhancers, as "the more promising existing drug treatments" for SDAT. (PTX-631 at 304) Dr. Murray Raskind, plaintiffs' expert, participated in clinical trials of oxiracetam, a piracetam analog. (D.I. 386 at 1106:9-1107:13)

59. In 1985, R.J. Wurtman of the Massachusetts Institute of Technology identified seven different "theoretical loci at which a drug might act to enhance cholinergic neurotransmission, and thereby possibly benefit patients with AD/SDAT": (1) post-synaptic agonists; (2) pre-synaptic (muscarinic) antagonists; (3) CIs; (4) pre-synaptic enhancement of the release of stored ACh; (5) pre-synaptic enhancement of ACh synthesis; (6) activation of excitatory receptors on cholinergic neurons; and (7) influencing the interactions of adenosine with pre- or post-synaptic receptors. (PTX-719) With respect to CIs, Dr. Wurtman noted that drugs like physostigmine that inhibit AChe everywhere "would have too many side-effects to be used clinically"; no drugs were known at that time that could affect cortical cholinergic synapses but not nerve synapses. (*Id*. at 277)

60. Most notably, Dr. Levey himself in 1985 observed this lack of specificity between receptor subtypes to be a problem with CIs. Dr. Levey suggested in 1985 that CIs "may not be beneficial" in treating AD due to their action at pre-synaptic auto-receptors. (PTX-1223 at 870; D.I. 384 at 301:12-306:12) He also noted that, at that time, the pharmaceutical industry began to focus on direct muscarinic agonists. (PTX-1223 at 870; D.I. 384 at 306:13-307:14) Dr. Levey personally viewed muscarinic agonists as the most promising approach (D.I. 384 at 300:5-7); this is the approach he took in attempting to develop an AD treatment.FN32 (*Id*. at 256:20-257:17) Also in 1985, Dr. Bartus, another lead researcher in this area, noted that "the available studies with cholinergic agents provide the optimist with a basis of hope for future drug development, but they admittedly offer no immediate promises of providing effective therapeutic

intervention." (PTX-632 at 343)

FN32. This testimony is consistent with that of plaintiffs' expert Dr. Coyle, who testified that the concern of side effects expressed by Professor Wurtman was widely shared in the AD field, causing many researchers to favor selective muscarinic agonists over CIs. (D.I. 386 at 880:11-885:13)

61. Despite some optimism in the field for the use of CIs, what can be surmised by the evidence is that several options were available to a person of skill in the art seeking to improve cognitive function in AD patients by improving ACh deficiency in 1986. Put another way, such a person could have, but would not necessarily have, begun with the intra-synaptic approach.

d. Prior art disclosed the use of galanthamine for different conditions

62. The disclosures of the prior art with respect to galanthamine generally fall into two categories: art disclosing that galanthamine could be used to increase cortical activity following brain damage; and art disclosing that galanthamine could be used to reduce the effects of scopolamine. Daskalov disclosed that a daily dose of between 3 and 20 mg of galanthamine is an AChe inhibitor that could be used to treat aphasia (due to brain injury). (PTX-743) In the context of discussing the restoration of cortical function following local brain damage, Luria noted that galanthamine was the strongest known CI and had a more marked and lasting effect than physostigmine. (PTX-744 at 5985) As discussed previously, Bhasker also suggested the use of CIs such as galanthamine in small doses to facilitate ACh activity in the brain in the context of arrested dementia. (DTX-483) Bhasker did not suggest using galanthamine to treat progressive dementia; contrarily, Bhasker taught away from such a use by stating that progressive dementia appeared to be unbeatable.FN33 (*Id*. at 12374) Each of these disclosures occurred between 1969 and 1981.

FN33. For reasons discussed previously, the court disagrees with defendants that Bhasker, standing alone, discloses all of the limitations of claim 1 of the '318 patent. Plaintiffs do not dispute that Bhasker, in combination with Daskalov and Cozanitis, disclose all the limitations of claim 1.

63. As discussed previously, both Cozanitis and Baraka disclosed that galanthamine could be used to reduce the effects of scopolamine. Cozanitis also disclosed that galanthamine was advantageous over physostigmine for this purpose due to its longer duration of action. (DTX-70 at 649) Baraka reported that the use of a galanthamine hydrobromide injection successfully reversed the effects of scopolamine overdosage. (DTX-71) Baraka also characterized galanthamine as an AChe inhibitor like physostigmine, with superior duration and efficacy. (*Id*.) Both articles were published in 1977.

64. Cozanitis's and Baraka's comments regarding the superiority of galanthamine occurred in the context of discussing treatment for scopolamine-induced dementia. Scopolamine is a drug that blocks the muscarinic receptor; its effects are rapidly reversible when the drug is metabolized. (D.I. 386 at 886:24-887:12) Scopolamine does not affect the cholinergic neurons. It does not mimic the degeneration in cholinergic neurons seen in AD patients or allow study of the resultant effect on nicotinic receptors. (*Id*.) Scopolamine-induced dementia is an acute condition, meaning that it is characterized by rapid onset and/or progression, as opposed to a long-term condition like progressive dementia. (D.I. 389 at 462:2-6; D.I. 386 at 886:24-888:8) In short, scopolamine mimics the symptoms of AD to some degree,FN34 but its usefulness as a model for AD research has limitations. Put another way, a person of skill in the art would not have a reasonable

expectation of success for using a drug that worked for scopolamine-induced delirium to treat AD. Physostigmine was approved by the FDA for the treatment of scopolamine-induced delirium (under the trade name Antilirium(R)). (D.I. 389 at 461:14-462:8) As Dr. Domino noted, physostigmine was safe and tolerable when used to treat scopolamine-induced delirium (the acute condition), but was not safe and tolerable when used to treat AD (the progressive condition). (D.I. 389 at 462:7-13)

FN34. As noted by Baraka, scopolamine can result in "central anticholinergic syndrome characterized by drowsiness, disorientation, delusions, and hallucinations." (DTX-71)

65. Unlike physostigmine, galanthamine was not approved by the FDA for treatment of scopolamine-induced delirium. Even assuming galanthamine and physostigmine were "very closely related" CIs,FN35 it does not follow that the successful use of galanthamine for AD (where physostigmine had failed) would have been obvious based on physostigmine's use for scopolamine-induced dementia. As defendants' experts confirmed, the failure of physostigmine for AD was widely attributed to its peripheral cholinergic effects. (PTX-752 ("Presently, physostigmine has limited usefulness due to its very short duration of action, less than one hour, and the high incidence of peripheral cholinergic side effects."); D.I. 384 at 174:21-25; D.I. 462:19-464:6) Galanthamine had an establishedtherapeutic use for treating peripheral nervous system diseases. (PTX-1181; D.I. 384 at 263:17-264:5 FN36) Another drug that acted in the periphery would have been an attractive candidate. (D.I. 386 at 915:7-10) However, not only did galanthamine work, but an unexpected benefit has been observed with galanthamine. In addition to increasing cholinergic function, galanthamine appears to impede the progress of the disease itself. (D.I. 389 at 494:16-496:18; D.I. 386 at 930:12-930:25,FN37 1170:17-1171:11) Though not insubstantial, the court finds that defendants' evidence of obviousness does not rise to the level of "clear and convincing" required to invalidate the '318 patent.

FN35. *See* Daiichi Sankyo Co., Ltd. v. Apotex, Inc., 501 F.3d 1254 (Fed.Cir.2007) (non-precedential) (cited by defendants at D.I. 396 at 29-30). In Daiichi, the undisputed trial testimony established that the antibiotic ciprofloxacin was a "very close relative" to ofloxacin. Id. at 1258. The court found that a prior art article teaching the successful use of ear drops of ciprofloxacin to treat middle ear infections rendered the patent at issue, directed to a method of treating bacterial ear infections by topically administering ofloxacin, obvious, in view of the proper determination of the level of skill in the art. Id. at 1258-59.

FN36. Dr. Levey agreed that Pernov disclosed galanthamine "as being above all peripheral and nicotinic." On cross-examination, Dr. Levey admitted that galanthamine's "use in the literature had been for peripheral nicotinic effect, myasthenia gravis," though he also claimed that galanthamine had known (non-specific) muscarinic properties. (D.I. 384 at 276:1-12)

FN37. Dr. Coyle testified that it is not ethically possible to do clinical trials to confirm these effects, insofar as such studies would necessitate the withholding of treatment from AD patients for the control group. (D.I. 386 at 931:1-9) This explanation reasonably justifies the lack of further evidence in support of this point.

e. Secondary considerations

66. In addition to an unexpected result, the court notes that other secondary considerations of

nonobviousness demonstrate that galanthamine was not an obvious treatment for AD. Others had tried other CIs, ACh precursors and direct muscarinic agents, and failed. Bhasker pre-dated Dr. Davis' invention by over a decade. Yet skepticism remained over the CI approach (PTX-714 at 419; PTX-632 at 343). In 1986, there remained a clear, long-felt but unmet need for a treatment for AD. Even as of 1989, the FDA was looking for a "substantive therapeutic advance." (PTX-1122) Finally, there can be little dispute that Razadyne(R), the embodiment of the '318 patent, has been a commercial success. It has grossed over $912 million dollars over the first five years of its sales. (D.I. 390 at 1376:11-15)

f. Conclusion

67. Based upon the foregoing, it is the opinion of the court that Dr. Davis did not "merely use[ ] routine research methods to prove what was already believed to be the case." PharmaStem, 491 F.3d at 1363. In the case at bar, a drug described in the art for the treatment of scopolamine induced delirium, peripheral diseases, or dementia following local brain injury was tried for AD, a progressive disease, one in which Bhasker had deemed untreatable, and which had been unsuccessfully treated with physostigmine, another peripheral CI. Taking a step backward, the intra-synaptic approach was not the only methodology being used in 1986. Dr. Wurtman identified seven different methodologies available to approach ACh deficiency. Dr. Levey agreed that "[t]here were many different ways being tried, even back in 1986," "logic led in a lot of different directions" with respect to addressing the cholinergic deficit, and "the consensus was many ways should be approached." (D.I. 384 at 299:18-300:24) It is unclear exactly how many CIs exist in total, but by 1999, at least 38 different CIs had been tried for AD. (*Id*. at 289:11-25; PTX-214) The court disagrees that "a finite number of identified, predictable solutions" existed to improve cognitive function in AD patients in 1986. Absent more, the court does not find in favor of defendants' "obvious to try" argument. *See* Takeda Chemical Indus., Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1359 (Fed.Cir.2007) ("[r]ather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation.").

4. Enablement

a. Defendant's motion to exclude the testimony of Dr. Raskind on enablement

68. At trial, Dr. Raskind testified for plaintiffs that the prior art cited in the '318 patent conveyed to a person of ordinary skill in the art that galanthamine could rectify the nicotinic cholinergic receptor deficit present in AD patients. (D.I. 390 at 1180:2-1182:7, 1183:9-1189:8, 1272:13-21) More specifically, Dr. Raskind testified that the animal lesion model disclosed in the patent results in a cholinergic deficiency at both nicotinic and muscarinic receptors, therefore, a person of ordinary skill in the art would understand the '318 patent to disclose that galanthamine was acting at both receptors. (*Id*. at 1185:18-1186:25) Defendants request that the court strike this testimony as outside of Dr. Raskind's expert report. (D.I. 396 at 46, n.31)

69. Dr. Raskind's second expert report, under the heading "ENABLEMENT," contains a statement that the '318 patent "outlines an approach for [AD] researchers to confirm the efficacy and tolerability of the invention by providing the steps appropriate for confirming Dr. Bonnie Davis' insight concerning galanthamine most significantly, the manner of carrying out animal testing to confirm the proposed efficacy." (D.I. 402, ex. B at para. 55) In his deposition, Dr. Raskind stated that the lesion model results in pre-synaptic cholinergic deficiency. (D.I. 402, ex. C at 181:2-13) He did not limit "cholinergic deficiency" to one type of receptor:

[Dr. Davis's knowledge of the endocrine window t]ogether with her knowledge that galanthamine had the

ability, at least to some degree, to increase the cholinergic activity in the central nervous system, and her knowledge that there was a cholinergic deficit in [AD], came to what I thought was [a] pretty brilliant conclusion[.]

(*Id*. at 107:17-108:10) Dr. Raskind also testified that lesions are characterized by numerous behavioral defects; "drugs that can normalize these abnormalities would have a reasonable expectation of efficacy in [AD]." (*Id*. at 184:2-10) Upon review of the documents and deposition testimony, the court finds that defendants were not prejudiced by Dr. Raskind's trial testimony on the issue. Fed.R.Civ.P. 26(a)(2)(B).

b. Enablement standard

70. The statutory basis for the enablement requirement is found in 35 U.S.C. s. 112, paragraph 1, which provides in relevant part:

The specification shall contain a written description of the invention and of the manner and process of making and using it, in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same.

71. The Federal Circuit has explained that "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable.... Tossing out the mere germ of an idea does not constitute enabling disclosure." Genentech, Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366 (Fed.Cir.1997).

[12] 72. To satisfy the enablement requirement, a specification must teach those skilled in the art how to make and to use the full scope of the claimed invention without undue experimentation. Genentech, 108 F.3d at 1365. "While every aspect of a generic claim certainly need not have been carried out by the inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." Id. at 1366. The specification need not teach what is well known in the art. Hybritech v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384 (Fed.Cir.1986).

[13] 73. Enablement is determined as of the filing date of the patent application. In re Brana, 51 F.3d, 1560, 1567 n. 19 (Fed.Cir.1995).

[14] 74. The use of prophetic examples does not automatically make a patent non-enabling. The burden is on one challenging validity to show, by clear and convincing evidence, that the prophetic examples together with the other parts of the specification are not enabling. Atlas Powder Co. v. E.I. du Pont De Nemours & Co., 750 F.2d 1569, 1577 (Fed.Cir.1984).

75. Some experimentation may be necessary in order to practice a claimed invention; the amount of experimentation, however, "must not be unduly extensive." Id. at 1576.

76. The test for whether undue experimentation would have been required is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.

PPG Indus. Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564 (Fed.Cir.1996) (quoting Ex parte Jackson, 217 U.S.P.Q. 804, 807 (1982)).

[15] 77. A court may consider several factors in determining whether undue experimentation is required to practice a claimed invention, including: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance disclosed in the patent; (3) the presence or absence of working examples in the patent; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (6) the predictability of the art; and (7) the breadth of the claims. In re Wands, 858 F.2d 731, 737 (Fed.Cir.1988). These factors are sometimes referred to as the "Wands factors." A court need not consider every one of the Wands factors in its analysis. Rather, a court is only required to consider those factors relevant to the facts of the case. *See* Amgen, Inc. v. Chugai Pharm. Co., Ltd., 927 F.2d 1200, 1213 (Fed.Cir.1991).

78. The enablement requirement is a question of law based on underlying factual inquiries. Wands, 858 F.2d at 737.

c. Discussion

[16] 79. As discussed previously, Dr. Davis did not have galanthamine when her patent application was filed; Dr. Coyle's experiments were not completed until after the '318 patent was allowed. Nevertheless, and despite Dr. Davis' offer to provide experimental data once it was obtained (PTX-14 at 2), the examiner allowed the application, implicitly finding that adequate evidence of utility existed. Defendants assert, in view of the minimal disclosure of the specification, that the '318 patent cannot be both non-obvious and enabled. That is, if no one would have believed that galanthamine would work as a treatment for AD, persons of ordinary skill in the art would not accept the statementsas to the effects of galanthamine "without question."

80. Defendants lift this language from Rasmusson v. SmithKline Beecham Corp., 413 F.3d 1318 (Fed.Cir.2005), wherein the Federal Circuit discussed the enablement requirement of s. 112, first paragraph, in the context of a pharmaceutical patent application. The claims at issue in Rasmusson were drawn to a method of treating a type of prostate cancer by administering a chemical compound called finasteride. Id. at 1320. Finasteride acts as a selective 5 alpha-reductase ("5-alpha-R") enzyme inhibitor, responsible for converting the hormone testosterone to dihydrotestosterone ("DHT"). Id. The applicant failed "to provide any data to demonstrate the effects of finasteride in treating prostate cancer." Id. at 1322. The applicant argued, however, that because "a person of ordinary skill in the art at the time of his applications would have believed that administering a therapeutically effective amount of finasteride could be used for treating human prostate cancer[,] ... he did not need to provide any data to demonstrate the efficacy of finasteride." Id. at 1323. The Federal Circuit found that substantial evidence supported the Board's decision that a person of ordinary skill in the art would not have had such a belief. Id. at 1324. Specifically, articles and testimony of record demonstrated that such a person would not know that 5-alpha-R inhibition had anti-tumor effects, "because it was not clear whether DHT or testosterone caused prostate cancer." Id. The Rasmusson court noted that, during prosecution, "it is proper for the examiner to ask for substantiating evidence unless one with ordinary skill in the art would accept the allegations as **obviously correct.**" Id. at 1323 (citations omitted) (emphasis added). Further, "where there is no indication that one skilled in the art would accept **without question** statements as to the effects of the claimed drug products and no evidence has been presented to demonstrate that the claimed products do have those effects, an applicant has failed to demonstrate sufficient utility and therefore cannot establish enablement." Id. (internal quotations and brackets omitted) (citing In re Novak, 49 C.C.P.A. 1283, 306 F.2d 924, 928 (1962)) (emphases added).

Defendants utilize these standards in making their argument that the '318 patent is not enabled.

81. Rasmusson was an appeal of a Board decision, and both of the aforementioned statements were made in the context of a patent application prior to issuance. The '318 patent, by contrast, is presumed valid and enabled unless proven otherwise by clear and convincing evidence. The question at bar is not, as defendants frame it, whether the specification leaves any doubt that galanthamine could have been used to treat AD; it is whether clear and convincing evidence demonstrates that the specification does not teach one of skill in the art how to use the claimed invention, i.e., whether a person of ordinary skill in the art could have, based on the disclosure of the '318 patent, practiced the invention without undue experimentation.

82. Notwithstanding the court's disagreement with defendants over the applicability of the "without question" language iterated in Rasmusson, the court finds that case instructive. The Rasmusson court observed that the applicant "did not make any contrary showing that a person of ordinary skill in the art as of the filing date of the third application would have recognized that a selective 5-alpha-R inhibitor in general, or finasteride in particular, would be effective in treating prostate cancer." Id. at 1324. In the case at bar, Dr. Davis stated that, even after conceiving of her invention and constructively reducing it to practice, she "certainly wasn't sure, and a lot of other people weren't sure[,] that [CIs] would ever work." (D.I. 389 at 712:14-17) As stated in Rasmusson,

[i]f mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to "inventions" consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked.

413 F.3d at 1325. Dr. Davis did not receive any confirming data until after the '318 patent was allowed. In view of the prior art disclosures regarding the flaws of physostigmine in AD treatment, discussed previously in the context of obviousness, it does not follow that a person of ordinary skill in the art, reading the '318 patent, would have recognized that galanthamine would be effective in treating AD in the absence of any experimental proof. *See* Application of Fisher, 57 C.C.P.A. 1099, 427 F.2d 833, 839 (1970) ("In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved."). Put another way, since plaintiffs rely exclusively on the prior art to establish enablement, FN38 the court agrees with defendants that the '318 patent cannot both be non-obvious and enabled.

FN38. "Here, because the patent provides data-in the form of galanthamine's effects as determined in prior experiments-and connects that data to show an **expectation** of utility through the animal lesion model as set forth in the patent, the requirements of section 112 are met." (D.I. 398 at 47) (emphasis added) Dr. Raskind's testimony on enablement focused on the disclosures of the pieces of prior art cited in the "Background Art" section of the patent. (D.I. 390 at 1180:10-1184:17) He then discussed the animal lesion model. (*Id*. at 1184:18-1189:23)

83. Claim 1 of the '318 patent contains no parameters for the administration of galanthamine to AD patients (aside from a "therapeutically effective amount"); claim 4 further requires the method of administration to be oral and in the range of 10-2000 mg per day. Plaintiffs assert that "galanthamine is an old compound for which extensive dosing information existed." (D.I. 398 at 43, n.19 (citing D.I. 384 at 230:21)) Additionally, Dr. Raskind testified that the standard clinical practice of dose titration could be used to find a

therapeutically effective dose of galanthamine. (D.I. 390 at 1178:23-1179:8) Even assuming this to be the case, this does not correct for the fact that the '318 patent only surmises how the claimed method could be used, rather than teach one of skill in the art how to use the claimed method.FN39 The ' 318 patent is, therefore, invalid for lack of enablement.

FN39. In view of "the complete absence of data supporting the statements which set forth the desired results of the claimed invention," the application which issued as the '318 patent likely should have been rejected by the examiner for lack of utility in addition to lack of enablement. In re Cortright, 165 F.3d 1353, 1356 (Fed.Cir.1999); *see also* Process Control Corp. v. HydReclaim Corp., 190 F.3d 1350, 1358 (Fed.Cir.1999) ("If a patent fails to meet the utility requirement because it is not useful or operative, then it also fails to meet the how-to-use aspect of the enablement requirement.").

III. CONCLUSION

84. For the reasons discussed above, the court concludes that defendants have failed to prove, by clear and convincing evidence, that the ' 318 patent is invalid as anticipated or obvious.

85. Defendants have proven, by clear and convincing evidence, that the '318 patent is invalid for lack of enablement.

ORDER

At Wilmington this 27th day of August, 2008, consistent with the opinion issued this same date;

IT IS ORDERED that:

1. Plaintiffs' motion for a temporary restraining order (D.I.412) is denied.

2. The clerk of court shall enter judgment in favor of defendants and against plaintiffs.

D.Del.,2008.
In re '318 Patent Infringement Litigation

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