NOT FOR PUBLICATION

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

TEVA NEUROSCIENCE, INC., TEVA PHARMACEUTICALS USA, INC., and TEVA PHARMACEUTICALS INDUSTRIES, LTD., Plaintiffs, v. WATSON LABORATORIES, INC., MYLAN PHARMACEUTICALS, INC., MYLAN INC., ORCHID CHEMICALS & PHARMACEUTICALS LTD., ORCHID HEALTHCARE (a division of Orchid Chemicals & Pharmaceuticals Ltd.) and ORGENUS PHARMA INC. Defendants.	Civil Action No. 2:10-cv-05078 Opinion
TEVA NEUROSCIENCE, INC., TEVA PHARMACEUTICALS USA, INC., and TEVA PHARMACEUTICALS INDUSTRIES, LTD., Plaintiffs, v. APOTEX CORP. and APOTEX INC. Defendants.	Civil Action No. 2:11-cv-3076

Claire C. Cecchi, U.S.D.J.

This matter comes before the Court by complaint of Teva Neuroscience, Inc., Teva Pharmaceuticals USA, Inc. and Teva Pharmaceuticals Industries, Ltd. (collectively, "Teva") against Mylan[1] and certain other defendants.[2] This case concerns the validity of United States Patent No. 5,453,446 ("the '446 Patent"), which is directed to a method of treating Parkinson's disease. This Court conducted a non-jury trial in this matter from May 15-31, 2013. This Opinion constitutes the Court's findings of fact and conclusions of law pursuant to Federal Rule of Civil Procedure 52(a). For the reasons stated herein, a finding in favor of Teva will be entered.

BACKGROUND

I. The Parties

Plaintiff Teva Pharmaceutical Industries Ltd. ("Teva Ltd.") is an Israeli company with its principal place of business at 5 Basel Street, Petach Ti.Kva, 49131, Israel. (Joint Pretrial Order, Stipulation of Facts ("SOF") ¶ 20.) Teva Ltd. is the sole owner of the '446 Patent. (Id.) Plaintiff Teva Neuroscience, Inc. ("Teva Neuroscience") is a Delaware corporation with its principal place of business at 901 E. 104th Street, Suite 900, Kansas City, Missouri 64131. (Id. ¶ 21.) Teva Neuroscience is a wholly-owned subsidiary of Teva Ltd. (Id.) Plaintiff Teva Pharmaceuticals USA, Inc. ("Teva USA") is a Delaware corporation with its principal place of

[1] "Mylan" consists of Mylan Pharmaceuticals, Inc., Mylan Inc. and Mylan LLC.

[2] These defendants included "Orchid," consisting of Orchid Chemicals & Pharmaceuticals Ltd., Orchid Healthcare (a division of Orchid Chemicals & Pharmaceuticals Ltd.), and Orgenus Pharma, Inc., "Watson," consisting of Watson Pharma and Watson Laboratories, Inc., and "Apotex," consisting of Apotex Corp. and Apotex Inc. Orchid, Watson and Apotex settled with Teva prior to the start of trial.

business at 1090 Horsham Road, North Wales, Pennsylvania 19454. (Id. ¶ 22.) Teva USA is a wholly-owned subsidiary of Teva Ltd. (Id.)

Defendant Mylan Inc. is a Pennsylvania corporation with its principal place of business at 1500 Corporate Drive, Canonsburg, Pennsylvania 15317. (Id. ¶ 29.) Defendant Mylan Pharmaceuticals Inc. is a West Virginia corporation with its principal place of business at 781 Chestnut Ridge Road, Morgantown, West Virginia 26505. (Id. ¶ 30.) Mylan Pharmaceuticals is a wholly-owned subsidiary of Mylan. (Id. ¶ 31.)

II. The '446 Patent

The '446 Patent, entitled "Use of the R-Enantiomers of N-Propargyl 1-Aminoindan Compounds for Treating Parkinson's Disease," was issued by the United States Patent and Trademark Office (the "PTO") on September 26, 1995. (Id. ¶¶ 38-40.)

Moussa B.H. Youdim, John P. M. Finberg, Ruth Levy, Jeffrey Sterling, David Lerner, Tirtsah Berger-Paskin and Haim Yellin are the inventors listed on the face of the '446 Patent. (Id. ¶ 42.) The named inventors assigned the '446 Patent to Teva Ltd. and the Technion Research and Development Foundation Ltd. ("Technion"). Technion subsequently assigned its rights to the '446 Patent to Teva Ltd. (Id. ¶¶ 45-46.)

The '446 Patent issued from Application No. 255,046 ("the '046 Application"), filed on June 7, 1994. (Id. ¶ 43.) The '046 Application is a continuation of Application No. 63,455 ("the '455 Application"), which was filed on May 18, 1993, and which issued as Patent No. 5,387,612 ("the '612 Patent") on February 7, 1995.[3] The '455 Application is a continuation of Application

[3] The '612 Patent claims the use of R(+)-PAI as monotherapy to treat Parkinson's disease. (PTX 332.)

No. 632,184 ("the '184 Application"), which was filed on December 21, 1990, and which claims priority to Israel Application No. 92952, filed January 3, 1990. (Id. ¶¶ 43-44.) The applicants submitted a terminal disclaimer for the '046 Application over the '612 Patent on February 28, 1995. (Id. ¶ 62.) The '446 Patent issued from the '046 Application on September 26, 1995. (Id. ¶¶ 62-63.) The '446 Patent expires on February 12, 2017. (Id. ¶ 41.)

Teva is asserting Claims 1, 2, 17, 18, and 19 of the '446 Patent in this litigation. (Id. ¶ 47.) The asserted claims read as follows:

Claim 1	A method of treating a subject for Parkinson's disease which comprises administering to the subject an amount of R(+)-N-propargyl-1-aminoindan or a pharmaceutically acceptable salt thereof effective to treat the subject.
Claim 2	The method of claim 1, wherein the R(+)-N-propargyl-1-aminoindan or a pharmaceutically acceptable salt thereof is administered orally.
Claim 17	The method of claim 1 which further comprises administering to the subject Levodopa in an amount relative to the amount of R(+)-N-propargyl-1-aminoindan or a pharmaceutically acceptable salt thereof effective to treat the subject.
Claim 18	The method of claim 1 which further comprises administering to the subject a decarboxylase inhibitor in an amount effective to ensure L-dopa uptake.
Claim 19	The method of claim 18, wherein the decarboxylase inhibitor is Carbidopa.

R(+)-N-propargyl-1-aminoindan is referred to herein as "R(+)-PAI." In 1994, the name rasagiline was adopted for R(+)-PAI. (Id. ¶¶ 47-49.)

R(+)-PAI is the R(+) enantiomer of N-propargyl-1-aminoindan.[4] (Tr. 61:5-14 (Ruffolo).) R(+)PAI has a chiral center (Tr. 63:25-64:3 (Ruffolo)), meaning that it contains a carbon atom that has four different groups of atoms attached to it. (Tr. 64:6-7 (Ruffolo).) "Molecules that have the same chemical substituents, but different spatial arrangements, are referred to as stereoisomers." Sanofi-Synthelabo v. Apotex, Inc., 470 F.3d 1368, 1372 (Fed. Cir. 2006).

[4] N-propargyl-1-aminoindan is also referred to as racemic PAI or AGN 1135.

"Enantiomers are a pair of stereoisomers that are non-superimposable mirror images of each other." Pfizer, Inc. v. Ranbaxy Labs. Ltd., 457 F.3d 1284, 1286 (Fed. Cir. 2006). This characteristic is "often likened to the relative structures of a person's right and left hands." Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 348 F. Supp. 2d 713, 720 (N.D.W.Va. 2004). Enantiomers are capable of rotating plane-polarized light. Enantiomers that rotate polarized light to the right are referred to as (+), and enantiomers that rotate polarized light to the left are referred to as (-). Id. at 720-21; Sanofi-Synthelabo, 470 F.3d at 1372. Enantiomers are also sometimes designated d- (dextrorotatory or right rotating) or l- (levorotatory or left rotating), again referring to the direction of optical rotation. Id. A racemate, or a racemic compound, is a 50/50 mixture of two mirror image enantiomers. (Tr. 65:17-18 (Ruffolo).) A racemic compound does not rotate light. (Tr. 65:19-25; 65:18-66:1 (Ruffolo).)

"Chemists also distinguish between enantiomers by designating an enantiomer as either 'R' or 'S' based upon the arrangement of certain atoms at the enantiomer's 'chiral center.' Where one enantiomer is an 'R,' the other will be an 'S.'" Ortho-McNeil, 348 F. Supp. 2d at 720- 21. In other words, the R and S enantiomer naming system simply allows scientists to distinguish and refer to enantiomers based on the orientation of groups of atoms around the chiral center. (Tr. 67:25-68:3; 68:1-4 (Ruffolo).)

In sum, the R(+)-PAI that is the subject of the '446 Patent is the enantiomer of the racemic compound PAI that has the R absolute configuration and that rotates light in the clockwise (+) direction. (Tr. 68:4-8 (Ruffolo).)

III. FDA Approval

Teva developed, applied for and obtained approval to make, sell, promote and/or market

Azilect®, a rasagiline mesylate tablet product. (SOF ¶ 64.) Azilect® was approved by the FDA and is indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease as both an initial monotherapy and also as an adjunct therapy to levodopa ("L-DOPA"). (SOF ¶¶ 64.)

Teva Ltd. is listed as the holder of New Drug Application ("NDA") No. 02-1641, under Section 505(a) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355(a), for 0.5 and 1.0 mg Azilect® tablets. (Id. ¶¶ 20, 65-66.) Teva Neuroscience is Teva Ltd.'s authorized U.S. agent for NDA No. 02-1641. (Id. ¶ 21.)[5] Teva Neuroscience and Teva USA have been selling, promoting, distributing and marketing Azilect® in the U.S. since July 2006. (Id. ¶ 68.) In 2006, the FDA granted New Chemical Entity exclusivity to Azilect®, which expired in May 2011. (Id. ¶¶ 51-52.)

Mylan filed an Abbreviated New Drug Application ("ANDA"), under 21 U.S.C. § 355(j), seeking FDA approval to market generic rasagiline mesylate tablets in .5 and 1.0 mg dosage strengths (the "generic tablets"). (See id. ¶¶ 76-78.) The generic tablets contain the active ingredient R(+)-PAI as the mesylate salt, and the draft labeling states that the products "are indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease as initial monotherapy and as adjunct therapy to levodopa." (See id. ¶¶ 98-100.)

Mylan's ANDA also contains a paragraph IV certification, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), alleging that the claims of the '446 Patent are invalid, unenforceable and/or would not be infringed by the manufacture, use, importation, sale or offer for sale of the

[5] Teva listed the '446 Patent in the U.S. Food and Drug Administration ("FDA") publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange

generic tablets described in the ANDA. (Id. ¶ 79.)

IV. Procedural History

On October 1, 2010, Teva filed suit against Mylan for infringement of the '446 Patent based on Mylan's submission of its ANDA. Mylan asserted counterclaims of non-infringement, invalidity and unenforceability of the '446 Patent. Prior to trial, Mylan stipulated that its use, offer to sell, importation, or sale of the proposed generic product described in its ANDA would directly infringe and/or actively induce and contribute to the infringement of Claims 1, 2, 17, 18 and 19 of the '446 Patent. (Stipulation and Order dismissing certain counterclaims and affirmative defenses, ECF No. 503.) Mylan also agreed to dismiss with prejudice its defense and counterclaim that the '446 Patent is unenforceable due to inequitable conduct. (Id.) Teva and Mylan both stipulated to dismiss with prejudice their claims that this is an exceptional case under 35 U.S.C. § 285. (Id.) Thus, the only remaining issue for trial was the validity of the '446 Patent.

V. Trial Experts

At trial, this Court heard testimony from a number of expert witnesses provided by Mylan and Teva.

A. Teva's Expert Witnesses

Teva presented the following witnesses at trial:

Dr. Robert Ruffolo has a Ph.D. in pharmacology and is the retired President of Research and Development and Corporate Senior Vice President for Wyeth Pharmaceuticals, now a part of Pfizer. (Tr. 40:16-17; 40:6-8 (Ruffolo).) Dr. Ruffolo is an expert in the fields of pharmacology,

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Book") as covering Azilect®. (Id. ¶ 50.)

stereochemistry, and drug discovery and development, and was personally involved in the development and discovery of over two dozen new drugs, including drugs to treat Parkinson's disease. (Tr. 40:4-6; 41:12-15 (Ruffolo).)

Professor Moussa Youdim is the first named inventor on the '446 Patent. (PTX 1.) Professor Youdim is a Distinguished Scientific Professor in the Department of Neurobiology at Yonsei University and a Professor Emeritus and Director of the Eve Topf Center of Excellence for Neurodegenerative Diseases at the Technion Israel Institute of Technology. (Tr. 81:18-21; 82:23-83:1; 82:16 (Youdim).)

Dr. Ruth Levy is a named inventor on the '446 Patent and a current employee of Teva. (Tr. 147:15-18; 147:24-25 (Levy).) Dr. Levy was the project leader for the development of Azilect® at Teva. (Tr. 148:23-149:10 (Levy).)

Dr. Peter Jenner has a Ph.D. in pharmacy and is an Emeritus Professor of Pharmacology at Kings College in London. (Tr. 635:17-19; 635:9-11 (Jenner).) For almost forty years, Dr. Jenner has studied, researched, taught, worked, and managed in the field of Parkinson's disease. (Tr. 635:11-13 (Jenner).)

Dr. Claire Henchcliffe has a Doctor of Philosophy degree from Oxford University, an M.D. from Columbia University and is a board-certified neurologist. (Tr. 1080:9-23 (Henchcliffe).) Dr. Henchcliffe is an Associate Professor in the Division of Movement Disorders, Department of Neurology and Neuroscience, at the Weill Medical College at Cornell University in New York City. She is also a Director of the Weill Cornell Parkinson's Disease and Movement Disorders Institute and an attending physician at the Weill Cornell Medical Center. (Tr. 1080:3-8 (Henchcliffe).)

Professor Jerry Hausman has a Doctor of Philosophy degree from Oxford University and is the McDonald Professor of Economics at the Massachusetts Institute of Technology. (Tr. 1208:8-15 (Hausman).)

B. Mylan's Expert Witnesses

Mylan presented the following witnesses at trial:

Dr. Neal Castagnoli is the Emeritus Peters Professor of Chemistry at Virginia Polytechnic Institute and State University ("Virginia Tech"). (DTX 1519; Tr. 267:1-5 (Castagnoli).) He is the former Co-Director of the Harvey W. Peters Research Center for the Study of Parkinson's Disease and Disorders of the Central Nervous System at Virginia Tech. (Tr. 267:1-5; 267:6-9 (Castagnoli).) Dr. Castagnoli earned his Ph.D. in Chemistry, his M.S. in Endocrinology and his B.S. in Chemistry from the University of California at Berkeley. (Tr. 267:17-21 (Castagnoli).) After graduating, he joined the University of California, San Francisco School of Pharmacy, where he was a Professor from 1966 until 1988. (Tr. 267:6-11; 267:23-268:3; 268:8-9 (Castagnoli).) From 1985 until 1988, Dr. Castagnoli was the Chairman of the Division of Toxicology at the UCSF School of Pharmacy. (DTX 1519.) Dr. Castagnoli's research activities have been focused on the molecular mechanisms of the MAO enzyme, including the role of MAO-B inhibitors in Parkinson's Disease. (Tr. 265:17-23 Castagnoli).)

Dr. Peter LeWitt is a Board-certified neurologist. (DTX 1467; Tr. 467:7 (LeWitt).) He currently serves as the Director of the Parkinson's Disease and Movement Disorders Program of the Henry Ford Health System. (Tr. 467:7-8; 468:7-10 (LeWitt).) He is also a full-time affiliate Professor of Neurology at Wayne State University, School of Medicine. (DTX 1467.) Prior to joining Henry Ford, Dr. LeWitt was the Associate Professor of Neurology at Wayne State

University School of Medicine (1984-1989), the Interim Chairman of Neurology at William Beaumont Hospital, Royal Oak, Michigan (2005-2006), the Director of the Clinical Neurosciences Center (2000-2006), and the Director of the Clinical Neuroscience Program at Sinai Hospital in Detroit (1988-1998). (DTX 1467; Tr. 469:21-24 (LeWitt).) Dr. LeWitt has more than 32 years of experience treating patients suffering from Parkinson's disease. (Tr. 470:1-2 (LeWitt).)

VI. Parkinson's Disease and Treatments

Parkinson's disease is a degenerative disease of the brain that results in motor movement disturbances. (Tr. 48:11-14 (Ruffolo).) It is characterized by symptoms such as uncontrollable tremors, muscle stiffness, gait problems, and at later stages, akinesia or the inability to move. (Tr. 48:11-14; 49:15-21 (Ruffolo).) Dopamine is one of the neurotransmitters in the brain that transmits signals necessary for the control of muscle movement. (Tr. 53:2-6 (Ruffolo).) The movement problems typically seen in Parkinson's disease are a result of the death of dopamine-producing neurons in the brain. (Tr. 52:17-53:2 (Ruffolo).) Reduced levels of dopamine in the brain are also responsible for the motor symptoms associated with Parkinson's disease. (Tr. 53:6-15 (Ruffolo).)

The Court's validity analysis must take into account the state of the relevant art in the treatment of Parkinson's disease as of January 3, 1990, the priority date of the '446 Patent. In early 1990 – and as of today – the most widely used treatment for Parkinson's disease was levodopa or L-DOPA. (Tr. 53:21-25; 54:13-18 (Ruffolo).) L-DOPA is a dopamine precursor, which means that it is converted into dopamine in the brain. (Tr. 54:20-23 (Ruffolo).) As such, L-DOPA helps relieve the symptoms of Parkinson's disease by replacing the dopamine that is

reduced in the brains of Parkinson's disease patients.[6] (Id.)

However, several problems are associated with L-DOPA treatment. (Tr. 55:14-16; 1092:12-21 (Ruffolo).) First, because L-DOPA is not a potent drug, very high doses of the drug are required. (Tr. 55:21-56:6 (Ruffolo).) As a result, patients taking L-DOPA must take several capsules at a time, up to six times a day. (Tr. 55:20-56:7 (Ruffolo).) This may be problematic for elderly patients. (Tr. 56:3-8 (Ruffolo).) Second, L-DOPA is also short-acting and somewhat unpredictable in terms of patient response. (Tr. 56:11-14 (Ruffolo).) This may make it difficult for physicians to determine a precise dose for their patients. (Id.) Third, L-DOPA therapy may cause side-effects such as nausea and vomiting. (Tr. 56:17-21 (Ruffolo).) Finally, and most importantly, after about two to five years of L-DOPA therapy, problems known as dyskinesias and the "on/off" phenomenon occur in patients. (Tr. 56:25-57:6 (Ruffolo); 1096:21-1097:16 (Henchcliffe).) Dyskinesias are involuntary and disabling muscle movements such as swaying back and forth and flailing of the arms. (Tr. 56:25-57:16 (Ruffolo).) The "on/off" phenomenon is a decreased response to L-DOPA therapy over time. (Tr. 56:22-57:6 (Ruffolo).) Specifically, during "on" times, a patient's symptoms are controlled, while during "off" times, they are not. (Tr. 1096:21-1097:16 (Henchcliffe).)

As discussed in more detail below, other relevant Parkinson's disease treatments in the late 1980s and early 1990 included dopamine agonists, pro-drugs of L-DOPA, Catechol-O-methyltransferase ("COMT") inhibitors and MAO-B inhibitors.

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[6] Dopamine cannot be administered directly to Parkinson's disease patients because it does not cross the blood-brain barrier and thus cannot penetrate the brain. (Tr. 55:1-9 (Ruffolo).) In contrast, L-DOPA crosses the blood-brain barrier, where it is then converted to dopamine. (Tr. 55:11-13 (Ruffolo).)

FINDINGS OF FACT AND CONCLUSIONS OF LAW

Having received documentary and testimonial evidence from the parties' experts, as well as substantial briefing on the various issues presented in this matter, the Court issues this Opinion which constitutes its findings of fact and conclusions of law with respect to the validity of the '446 Patent.[7]

OBVIOUSNESS

Mylan asserts that the '446 Patent is invalid for obviousness. Mylan argues that based on both the prior art knowledge regarding racemic PAI (AGN 1135) and the success of another similar MAO-B inhibitor in the treatment of Parkinson's disease, Teva developed the '446 Patent "through the predicable application of routine steps, none of which were inventive, rendering the patent invalid as obvious." (Mylan's Post-Trial Brief, Docket No. 525, ("MPTB"), 1.) Teva responds that the method claimed in the '446 Patent is not obvious because Mylan has not proven by clear and convincing evidence that: 1) in 1990, a POSA would have selected AGN 1135 as a lead compound for a new drug to treat Parkinson's disease; 2) in 1990, a POSA would have been motivated to combine the prior art references to obtain R(+)-PAI with a reasonable expectation of success; or 3) that the invention of the '446 Patent was obvious to try. Teva additionally argues that the objective evidence further demonstrates that the method claimed in the '446 Patent was not obvious.

I. Applicable Law

Under 35 U.S.C. § 103(a), a party may not obtain a patent "if the differences between the

[7] Although Teva argues that the '446 Patent is not anticipated, Mylan did not focus on any argument regarding anticipation in its post-trial briefs. Mylan has not shown that the '037 Patent

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 to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made." An issued patent is presumed valid, however, and "included within the presumption of validity is . . . a presumption of nonobviousness." Structural Rubber Prods. Co. v. Park Rubber Co., 749 F.2d 707, 714 (Fed. Cir. 1984).

"A party seeking to invalidate a patent based on obviousness must demonstrate by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." Procter & Gamble Co. v. Teva Pharms. USA, Inc., 566 F.3d 989, 994 (Fed. Cir. 2009) (internal quotation omitted). An invention may also be found obvious when it would have been "obvious to try"— i.e., "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions." KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 421 (2007); Eisai Co. v. Dr. Reddy's Labs., Ltd., 533 F.3d 1353, 1359 (Fed. Cir. 2008).

The Supreme Court has enumerated four factors to be considered by courts to determine whether an invention is obvious. Takeda v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (citing Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966)). These four factors are: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed subject matter and the prior art; and (4) secondary considerations, or "objective indicia of non-obviousness." Id.; see also KSR, 550 U.S. at 405.

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or any other prior art anticipates the '446 Patent.

The "objective indicia" of non-obviousness include, but are not limited to: meeting a long-felt need, the inventors' success despite the failure of others, commercial success, copying, praise and recognition for the invention, unexpected results, and significant effort and serendipity. See Ruiz v. A.B. Chance Co., 234 F.3d 654, 660-62 (Fed. Cir. 2000); see also Procter & Gamble, 566 F.3d at 994 (Fed. Cir. 2009). A court must make findings of fact and conclusions of law as to each of these Graham factors.

II. Scope and Content of the Prior Art

This Court will first define the scope and content of the prior art. As stated above, the relevant scope and content of the prior art is to be assessed as of the January 3, 1990 priority date of the '446 Patent. (PTX 1.)

A. Scope – Generally

As an initial matter, the parties contest the scope of the relevant art. Mylan argues that the relevant prior art should be limited to the "extensive study of the both the laboratory and therapeutic uses of MAO-B inhibitors, including (-) deprenyl and racemic PAI, extensive literature on the reasons to separate and evaluate racemic mixtures, including FDA guidelines, and the extensive literature as to the techniques to separate racemic compounds generally and racemic PAI specifically." (Mylan's Proposed Findings of Fact ("MPFF") ¶ 97.) Because Mylan views the problem to be overcome by the '446 Patent as "finding an MAO-B inhibitor that improved on the properties of (-) deprenyl, specifically by removing (-) deprenyl's amphetamine metabolite," (MPFF ¶ 106), Mylan argues that other classes of compounds that were being developed for Parkinson's disease in 1990 are not analogous art. (MPFF ¶¶ 108-113). In response, Teva posits that the scope of the analogous prior art includes all new chemical

compounds that were being investigated as possible treatments for Parkinson's disease. (Teva's Proposed Findings of Fact ("TPFF") ¶¶ 136-137.) Teva further argues that limiting the scope of the relevant art to only MAO-B inhibitors, as Mylan suggests, would reflect improper hindsight bias.

The Court agrees with Teva. In determining the scope and content of the prior art, the court must consider "the prior art as a whole." Panduit Corp. v. Dennison Mfg. Co., 810 F.2d 1561, 1567 n.37, 1568 (Fed. Cir. 1987). As such, courts must construe the scope of analogous prior art broadly. Wyers v. Master Lock Co., 616 F.3d 1231, 1238 (Fed. Cir. 2010) (citing KSR Int'l Co. v. Teleflex, Inc., 550 U.S. 398, 402 (2007)).

Further, "[a] reference qualifies as prior art for a determination under § 103 when it is analogous to the claimed invention." Innovention Toys, LLC v. MGA Entm't, Inc., 637 F.3d 1314, 1321 (Fed. Cir. 2011) (citation omitted). "Two separate tests define the scope of analogous art: (1) whether the art is from the same field of endeavor, regardless of the problem addressed, and (2) if the reference is not within the field of the inventor's endeavor, whether the reference still is reasonably pertinent to the particular problem with which the inventor is involved." Id. (citing In re Bigio, 381 F.3d 1320, 1325 (Fed. Cir. 2004)). "A reference is reasonably pertinent if . . . it is one which, because of the matter with which it deals, logically would have commended itself to an inventor's attention in considering his problem." Id. (citation omitted). Therefore, "[i]f a reference disclosure has the same purpose as the claimed invention, the reference relates to the same problem, and that fact supports use of that reference in an obviousness rejection." Id. Whether a prior art reference is "analogous" is a question of fact. Id.

Here, the invention is directed to a method of treating Parkinson's disease. (PTX 1, Claim 1) ("A method of treating a subject for Parkinson's disease which compromises administering to the subject an amount of . . .") As such, the prior art encompasses any and all references concerning possible new treatments for Parkinson's disease. See Daiichi Sankyo Co., Ltd. v. Apotex, Inc., 501 F.3d 1254 (Fed. Cir. 2007) (explaining that with regard to a patent drawn to a method for treating bacterial ear infections by administering an antibiotic to the ear, the prior art related broadly to the creation of a compound to treat ear infections without damaging a patient's hearing); Eli Lilly & Co. v. Actavis Elizabeth LLC, 731 F. Supp. 2d 348, 357-364 (D.N.J. 2010), rev'd in part on other grounds, 435 F. App'x. 917 (Fed. Cir. 2011), (explaining that for a patent claiming a method of treating attention-deficit/hyperactivity disorder, the scope of the prior art included all four of the main classes of drugs that were being used to treat ADHD before the priority date of the patent).

Further, to limit the prior art to only MAO-B inhibitors, the particular solution that the patentees devised to address the problem of treating Parkinson's disease, is to engage in improper hindsight reasoning. See Ecolochem, Inc. v. Southern California Edison Co., 227 F.3d 1361, 1372 (Fed. Cir. 2000) (clarifying that "defining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness"); AstraZeneca Pharms. LP v. Anchen Pharms., Inc., No. 10-cv-1835, 2012 U.S. Dist. LEXIS 43989, at *55 (D.N.J. Mar. 28, 2012) (explaining that "the Federal Circuit has admonished against the use of the claimed invention to define the prior art" because "[b]y importing the ultimate solution into the problem facing the inventor, the district court adopt[s] an overly narrow view of the scope of the prior art"). As such, the Court finds that the scope of the analogous prior art includes all drug

compounds that were being investigated for possible use to treat Parkinson's disease as of 1990. Specifically, these compounds included dopamine agonists, L-DOPA pro-drugs, COMT inhibitors and MAO-B inhibitors. The Court will now examine each in turn.

B. Dopamine Agonists

At trial, Teva presented evidence from Dr. Jenner indicating that dopamine agonists were a primary focus of research and development activity in 1990 by those seeking to discover a new drug to treat Parkinson's disease. (Tr. 645:4-7 (Jenner).) Dr. Jenner testified that researchers were interested in dopamine agonists because these compounds directly stimulate dopamine receptors and therefore were thought to offer the most direct way to transmit the electrical signals necessary for the control of motor movement. (Tr. 645:8-16 (Jenner).) Dr. Ruffolo further explained that dopamine agonists will continue to work even as the dopaminergic neurons in the brain are dying. (Tr. 58:15-19 (Ruffolo).)

Dr. Jenner and Dr. Henchcliffe both testified that there were two dopamine agonists approved for use in the United States prior to 1990 – bromocriptine and pergolide – both of which caused side effects (Tr. 648:23-649:10 (Jenner); 1104:20-1105:4 (Henchcliffe)) based on the fact that these compounds were derivatives of the ergot fungus. (Tr. 649:13-650:11 (Jenner).) As such, Dr. Jenner testified that a POSA in 1990 would have been motivated either to modify the known ergot derivative dopamine agonist compounds in an effort to reduce their side effects or to look for non-ergot derivative compounds that also functioned as dopamine receptor agonists. (Tr. 650:12-25 (Jenner).)

Finally, Dr. Jenner testified that several pharmaceutical companies were investigating dopamine agonists in the late 1980s, including Sandoz, Eli Lilly, Schering A.G., Merck Sharp &

Dohme, Smith Kline & French, Roussel UCLAF, and Lundbeck & Co. (Tr. 648:13-22 (Jenner)), and that these pharmaceutical companies were investigating both modifications to ergot derivative dopamine agonists and non-ergot derivative dopamine agonists as possible new treatments for Parkinson's disease. (Tr. 650:1-2; 651:1-5; 653:2-7; 17-21 (Jenner); PTX 44; PTX 54; PTX 66; PTX 124; PTX 125; PTX 126; PTX 133; PTX 149; PTX 153; PTX 155; PTX 157; PTX 159; PTX 161; PTX 167; PTX 170; PTX 171; PTX 173; PTX 174; PTX 184.)

According to Dr. Jenner, at least five of the dopamine agonists that were being investigated in the late 1980s were subsequently approved for use in the treatment of Parkinson's disease, including cabergoline, ropinerole, pramipexole, apormorphine and rotigotine. (Tr. 657:7-13 (Jenner).)[8]

C. Pro-drugs of L-DOPA

Pro-drugs of L-DOPA are also included within the scope of the relevant prior art. At trial, Dr. Jenner testified that, as of 1990, pro-drugs of L-DOPA offered potential as new drugs to treat Parkinson's disease. (Tr. 672:19-25 (Jenner).) As explained above, L-DOPA is converted into dopamine in the brain. However, L-DOPA has a short duration of effect and produces unwanted side effects. (Tr. 55:13-56:21 (Ruffolo).)

Dr. Ruffolo explained that a pro-drug is a derivative of L-DOPA that is first converted to L-DOPA before being transformed to dopamine in the brain. (Tr. 58:20-25 (Ruffolo).) Dr. Jenner testified that L-DOPA pro-drugs were of interest because, when effective, they exhibit

[8] The Court takes into consideration Mylan's argument that several of the dopamine agonists cited by Dr. Jenner were also reported to have orthostatic hypotension as a side effect.

increased bioavailiabity and brain penetration, thus allowing more L-DOPA to reach the brain. (Tr. 673:1-17 (Jenner).) Dr. Ruffolo further testified that these pro-drugs can increase the duration of action of L-DOPA and therefore result in a more even exposure of the patient to L-DOPA. (Tr. 58:20-59:1 (Ruffolo); 673:13-23 (Jenner).) Finally, Dr. Jenner testified regarding the pharmaceutical companies that were investigating pro-drugs of L-DOPA as of 1990. (Tr. 674:22-675:5 (Jenner).) He explained that Merck Sharp & Dohme developed a L-DOPA pro-drug, MB-355, which was reported in 1989 to have a prolonged duration of effect, thereby allowing a reduction in the number of daily doses of L-DOPA while also producing a more even patient response. (Tr. 675:6-23 (Jenner); PTX 183.) Additionally, Chiesi was marketing a L-DOPA pro-drug in Europe at that time. (Tr. 678:16-21 (Jenner).)

D. COMT Inhibitors

Catechol-O-methyltransferase ("COMT") inhibitors are also part of the relevant prior art. At trial, Dr. Jenner testified that COMT inhibitors were being actively investigated as drugs to treat Parkinson's disease as of 1990. (Tr. 679:14-22 (Jenner).) As Dr. Ruffolo explained, COMT is an enzyme that metabolizes L-DOPA before it reaches the brain and thus inactivates L-DOPA. (Tr. 59:2-8 (Ruffolo).) If the COMT enzyme is inhibited, more L-DOPA reaches the brain. (Tr. 59:2-8 (Ruffolo); 679:24-680:22 (Jenner).) Dr. Jenner testified that, in the late 1980s, there was particular interest in a new class of COMT inhibitors – 3-nitrocatechols – that were considered more selective than prior art COMT inhibitors. (Tr. 681:5-18 (Jenner).) Further, Dr. Jenner stated that at least two pharmaceutical companies, Hoffman-LaRoche and Orion, were actively investigating three different COMT inhibitors, entacapone, nitecapone and tolcapone, in

this new class. (Tr. 681:19-682:20 (Jenner); PTX 129; PTX 162; PTX 163.) Tolcapone and entacapone were subsequently approved for use in many countries. (Tr. 683:19-21 (Jenner).)

E. MAO-B Inhibitors

The final class of compounds included within the scope of the relevant prior art are MAO-B inhibitors. By 1990, it was known that the MAO enzyme, which exists in two different forms, MAO-A and MAO-B, was involved in the metabolism of dopamine. (Tr. 59:11-15 (Ruffolo).) Specifically, it was known that the MAO-B enzyme binds with dopamine and renders it inactive. (Tr. 59:25-60:21; PTX 6001 at P-demo-RR-15-17.) By inactivating dopamine, the MAO-B enzyme decreases dopamine levels in the brain, which results in an increase in the symptoms of Parkinson's disease. (Tr. 52:17-53:14 (Ruffolo).) MAO-B inhibitors treat the symptoms of Parkinson's disease by preventing the MAO-B enzyme from inactivating dopamine. (Tr. 59:12-15; 59:25-60:212 .)

Two MAO-B inhibitors are relevant to this action – (-) deprenyl and AGN 1135 (or racemic PAI). Both deprenyl and AGN 1135 are chiral structures, meaning they consist of two enantiomers, as described in detail above. (Tr. 63:25-64:2; 64:3-15 (Ruffolo); 295:14-296:15 (Castagnoli); DTX 1004 at 377.) MAO-B enzymes are also chiral in nature. (Tr. 281:21-283:9.) Because of the chirality of the MAO-B enzyme and MAO-B inhibitors, each enantiomer of an MAO-B inhibitor is expected to bind to the MAO-B enzyme in a different manner. (Tr. 281:21-283:9 (Castagnoli).)

1. (-) Deprenyl

The racemic compound deprenyl was first developed in 1966 by Dr. Joseph Knoll. (DTX 1004 (Knoll 1967).) Subsequently, Dr. Knoll and his colleagues investigated the enantiomers of

racemic deprenyl and established that the (-) deprenyl enantiomer[9] was 500 times more potent than (+) deprenyl in its inhibition of MAO. (DTX 1004 at 384). In 1985, it was noted that (-) deprenyl had the "R" absolute configuration and that (-) deprenyl was highly selective for MAO-B rather than MAO-A. (DTX 1065 at 4107, Table 1; Tr. 292:16-293:12, 327:9-22 (Castagnoli).) The prior art also taught that (-) deprenyl was known not to cause the "cheese effect." (DTX 1043 at 387.) The cheese effect is a sudden rise in blood pressure which occurs when foods high in tyramine, such as aged cheeses or red wine, are consumed when a MAO inhibitor is also in the body. This sudden spike in blood pressure can lead to a stroke, which can be fatal. (Tr. 701:20-702:3 (Jenner); 270:20-271:1 (Castagnoli).) Prior to 1990, it was discovered that that the cheese effect resulted from the inhibition of MAO-A, the form of the enzyme responsible for the metabolism of tyramine in the gut. (DTX-1043 at 388.)

Clinical studies in 1989 indicated that (-) deprenyl was a safe drug in patients with early, untreated Parkinson's disease, that early (-) deprenyl therapy delayed the need for treatment with L-DOPA, and that (-) deprenyl appeared to slow the rate of progression of Parkinson's disease. (DTX 1142 at 521; PTX 655.) Finally, it was established by 1990 that MAO-B inhibitors such as (-) deprenyl were effective in the MPTP model, which offered a prospect of neuroprotection. (DTX 1066; DTX 1043; DTX 1074.) MPTP refers to 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine, a neurotoxin that produces a parkinsonian-like syndrome in humans. The FDA approved (-) deprenyl in 1989. (See Tr. 308:2-8; 328:5-10 (Castagnoli); see also DTX 1317 (2008 version of deprenyl label).)

[9] (-) deprenyl is also referred to as selegiline.

(-) Deprenyl was closely examined in the DATATOP study, a clinical study which appeared in the November 1989 issue of the New England Journal of Medicine. (PTX 655.) According to the testimony of both Dr. Castagnoli and Dr. LeWitt, the DATATOP study established that MAO-B inhibitors such as (-) deprenyl were effective as a monotherapy for Parkinson's disease. (PTX 655 at 1367-68; Tr. 304:7-307:5 (Castagnoli); Tr. 512:6-15 (LeWitt).) According to Dr. Castagnoli, the DATATOP study indicated that MAO-B inhibitors offered a hope for neuroprotection in the treatment of Parkinson's disease. (Tr. 332:9-16 (Castagnoli); PTX 655.) Dr. Castagnoli further explained that the DATATOP study would have "encouraged a POSA to pursue avenues to generate potent, selective, irreversible, and safe [MAO-B inhibitors] to use in Parkinson's patients." (Tr. 305:12-14; 306:25-307:5 (Castagnoli).)

2. AGN 1135

a. The Prior Art Patents

In addition to (-) deprenyl, AGN 1135 (racemic PAI) is a MAO-B inhibitor relevant to the Court's analysis. AGN 1135 was first claimed in U.S. Patent No. 3,253,037 ("the '037 Patent"), entitled "N-2-alkynyl-Amino-Benzocyclo-Alkanes," which issued on May 24, 1966. (DTX 1103 Col. 15, II. 15-31.) The '037 Patent disclosed the synthesis of numerous compounds, including AGN 1135. AGN 1135 is specifically disclosed in Example 9 and claimed in claim 4. (DTX 1003 at 15:15-31, 19:13.) The '037 Patent taught that the disclosed compounds, including AGN 1135, may be administered orally, do not show blood pressure raising effects and are useful in treating depression. (DTX 1003 at 17:55-65, 4:48-66.) The '037 Patent also disclosed that AGN 1135 is a MAO inhibitor. (DTX 1103 Col. 4, 11. 48-50; Tr. 814:20-22, 814:23-815:3 (Ruffolo); Tr. 310:13-14 (Castagnoli).) Finally, the '037 Patent taught

that the racemates of the claimed compounds "may be resolved into the optically active d- and l-forms according to known resolution procedures," including the use of tartaric acid. (DTX 1003 at 9:51-53, 9:58-60.)

With regard to the disclosures of the '037 Patent, Dr. Ruffolo testified that the patent did not actually describe a method of treating a subject for Parkinson's disease. (Tr. 813:25-814:13 (Ruffolo).) Although the '037 Patent disclosed that the compounds claimed therein could be used as "stimulating agents in the treatment of fatigue, depression, and the like," it did not mention Parkinson's disease in particular. (DTX 1003 col.4, ll. 64-66; Tr. 813:25-814:4 (Ruffolo).) Dr. Ruffolo further explained that although some Parkinson's disease patients also have depression, there is no mention in the patent of the involuntary muscle disturbances and motor dysfunction that characterize Parkinson's disease. (Tr. 814:9-19 (Ruffolo).)

Dr. Ruffolo also pointed out that the '037 Patent did not actually describe the separation, isolation or characterization of the enantiomers of AGN 1135. (Tr. 841:23-842:1 (Ruffolo).) Finally, Dr. Ruffolo explained that although the '037 Patent disclosed that the compounds claimed therein, including AGN 1135, are MAO inhibitors generally, it did not disclose that the compounds are MAO-B inhibitors. (DTX 1003 col.4, ll. 48-50; Tr. 814:20-22 (Ruffolo).) Because the two forms of the MAO enzyme had not been identified at the time the '037 Patent issued, the patent drew no distinction between inhibition of the MAO-A enzyme versus inhibition of the MAO-B enzyme. (Tr. 310:13-14 (Castagnoli); 814:23-815:3 (Ruffolo).) Indeed, even Dr. Castagnoli admitted that a POSA reading the '037 Patent in 1990 would not have known if AGN 1135 was a selective inhibitor of the MAO-B form of the enzyme. (See Tr. 310:13-14 (Castagnoli).)

AGN 1135 was also identified in another relevant prior art patent, U.S. Patent No. 3,513,244 ("the '244 Patent"), entitled "Method of Lowering Blood Pressure By Administering Secondary and Tertiary Amines." The '244 Patent issued on May 19, 1970 and taught the use of AGN 1135 for the treatment of hypertension. (DTX 1011 Ex. 1, 5:49-64; 4:55-64.) The '244 Patent disclosed that patients who were orally administered 480 mg per day of AGN 1135 for two weeks had a marked lowering of blood pressure during this period. (DTX 1011 at 5:74-6:4.) The '244 Patent also taught the preparation of pharmaceutically acceptable salts, including mesylate salts. (DTX 1011 at 4:5-16.)

Teva's experts testified, however, that similar to the '037 Patent, the '244 Patent did not disclose that AGN 1135 could be used as a treatment for Parkinson's disease. In addition, the '244 Patent described AGN 1135's marked blood pressure lowering effect. (Tr. 703:22-705:15 (Jenner); 822:17-824:23 (Ruffolo).) Both Dr. Ruffolo and Dr. Jenner testified that Parkinson's disease patients were known to suffer from orthostatic hypotension, a condition in which blood pressure drops suddenly when the person goes from a lying or sitting position to standing upright. (Tr. 704:3-12 (Jenner); 823:16-824:10 (Ruffolo).) Dr. Ruffolo also testified that the '244 Patent did not identify how many persons were given AGN-1135 or whether they were healthy at the time the drug was given or were already suffering from high blood pressure. (DTX 1011 5:1-74 – 6:1-4; see also Tr. 825:10-24 (Ruffolo).) [10]

[10] The Court also considers Dr. Castagnoli's testimony that a POSA would recognize from the '244 Patent that AGN 1135 is safe even at doses much higher than the therapeutically relevant doses for treatment of Parkinson's disease. (Tr. 308:12-309:17 (Castagnoli); Tr. 331:18-24 (same).) Further, Dr. LeWitt testified that orthostatic hypotension can be managed by a patient

b. Prior art references comparing AGN 1135 to (-) deprenyl

In addition to the '037 and '244 Patents, several articles regarding AGN 1135 are also part of the relevant prior art.

In 1980, Finberg, et al. authored an article entitled "Pharmacology of selective propargyl "suicide" inhibitors of monoamine oxidase," which appeared in the publication *Enzyme and Neurotransmitters in Mental Disease*. ("Finberg 1980") (DTX 1032.) Finberg 1980 taught that MAO inhibitors have potential therapeutic value in the treatment of Parkinson's disease. Finberg 1980 further explained that (-) deprenyl was a selective MAO-B inhibitor and was useful as adjunct therapy with L-DOPA. According to the article, (-) deprenyl's clinical usefulness in the treatment of Parkinson's disease could be attributed to the fact that the human brain mainly contains the MAO-B form of the MAO enzyme. (DTX 1032 at 205, 206, 216; Tr. 125:20-127:5; Tr. 315:10-316:7, 316:24-317:18 (Castagnoli).) Finberg 1980 also explained that further animal and clinical studies would be required to determine the clinical value of the MAO-B inhibitor AGN 1135. Finally, Finberg 1980 concluded that the work described therein with AGN 1135 demonstrated that new MAO inhibitors, which offered an improvement on (-) deprenyl, could be developed and could prove effective in the treatment of depression and Parkinson's disease. (DTX 1032 at 216; Tr. 127:2-128:1 (Youdim).)

Also in 1980, Youdim, et al. authored an article entitled "The use of selective MAO type B inhibitors in the treatment of Parkinson's disease," which appeared in the publication *Enzyme and Neurotransmitters in Mental Disease*. ("Youdim 1980") (DTX 1033.) Like Finberg 1980, Youdim 1980 taught that selective MAO-B inhibitors were useful in the treatment of

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consuming more water or salt. (Tr. 486:1-11 (LeWitt).)

Parkinson's disease and that (-) deprenyl, which did not potentiate the tyramine pressor effect, was an effective adjunct therapy to L-DOPA, especially in patients who exhibited the on/off phenomenon. Youdim 1980 posited that "[t]his new and successful approach in the treatment of [Parkinson's disease] should be extended to other MAO-B inhibitors, e.g. AGN 1135 which has similar pharmacological actions to deprenyl but without deprenyl's amphetamine-like property." (DTX 1033 at 346, 348, 353; Tr. 117:16-118:8, 119:2-6 (Youdim); Tr. 530:16-531:18 (LeWitt).)

Subsequently, in 1981, Finberg et al. authored "Tyramine antagonistic properties of AGN 1135, An irreversible inhibitor of monoamine oxidase type B." ("Finberg 1981") (DTX 1042.) Finberg 1981 taught that 80% of the MAO activity in the brain was MAO type B and that MAO-B inhibitors have potential therapeutic value because of this fact. Finberg 1981 also disclosed that the use of (-) deprenyl in combination with L-DOPA was an effective treatment for Parkinson's disease, and that AGN 1135 had similar biological properties to (-) deprenyl, without the amphetamine-like effects. (DTX 1042 at 31, 34, 41; Tr. 332:19-333:4 (Castagnoli).)

Finberg, et al. issued a second article in 1981 entitled "Tyramine antagonistic properties of AGN 1135, An irreversible inhibitor of monoamine oxidase type B." ("Finberg II 1981") (DTX 1034.) Finberg II 1981 discussed animal pharmacological experiments comparing (-) deprenyl, AGN 1133 and AGN 1135. Finberg II 1981 taught that AGN 1135 was a selective inhibitor of MAO-B that did not potentiate the cheese effect and did not possess the intrinsic amphetamine-like activity of (-) deprenyl. (DTX 1034 at 65, 66, 70; Tr. 120:4-121:2 (Youdim).)

Kalir, et al. also authored an article in 1981, entitled "Selective acetylenic 'suicide' and reversible inhibitors of monamine oxidase types A and B." ("Kalir 1981") (DTX 1044.) Kalir 1981 taught that MAO-B inhibitors were useful as adjuncts to L-DOPA therapy in the treatment

of Parkinson's disease. Kalir 1981 further posited that AGN 1133 and AGN 1135 were of interest because both compounds were selective irreversible inhibitors of MAO-B; however AGN 1135 was more attractive because it demonstrated greater selectivity for MAO-B than AGN 1133 and possessed a tyramine antagonistic effect similar to that described for (-) deprenyl. (DTX 1044 at 55, 60; Tr. 121:16-123:6; 123:24-124:1 (Youdim); Tr. 318:14-20 (LeWitt).)

In 1985, Finberg, et al. published "Modification of blood pressure and nictitating membrane response to sympathetic amines by selective monoamine oxidase inhibitors, types A and B, in the cat." ("Finberg 1985") (DTX 1062; PTX 47.) Finberg 1985 compared the MAO inhibitors clorgyline and (-) deprenyl with AGN 1135. Finberg 1985 found that the tyramine pressor response was potentiated by clorgyline (a MAO-A inhibitor) but not by (-) deprenyl and AGN 1135 (selective MAO-B inhibitors). Finberg 1985 posited that AGN 1135, like (-) deprenyl, could be a useful drug in potentiating the action of L-DOPA in the treatment of Parkinson's disease. Finberg 1985 further explained that increasing the dosage of AGN 1135 could potentiate the cheese effect, while increasing the dosage of (-) deprenyl could produce sympathomimetic effects. (DTX 1062 at 544-545; Tr. 526:1-527:4 (LeWitt).)

Also in 1985, Heikkila, et al. authored "Prevention of MPTP-induced neurotoxicity by AGN 1133 and AGN 1135, selective inhibitors of monoamine oxidase-B." ("Heikkila 1985") (DTX 1066.) Heikkila 1985 taught that both AGN 1135 and (-) deprenyl were selective MAO-B inhibitors free of the cheese effect, and that AGN 1135 was a more potent inhibitor of MAO-B than (-) deprenyl. Heikkila 1985 also explained that AGN 1135 was protective against MPTP-induced toxicity in mice and that patients treated with (-) deprenyl and L-DOPA had a significant prolongation of their life span compared to those patients treated with L-DOPA alone. Finally,

Heikkila 1985 posited that MAO-B may play a role in the pathogenesis of Parkinson's disease and that AGN 1135 was attractive as a potential therapeutic agent in treating the disorder. (DTX 1066 at 313, 315, 316; Tr. 133:6-136:11 (Youdim); Tr. 528:8-530:15, 532:9-533:3 (LeWitt); Tr. 320:22-321:9, 331:4-9, 332:9-16, 357:22-358:9 (Castagnoli).)

Later, in 1986, Youdim, et al. published "MAO type B inhibitors as adjunct to L-dopa therapy." ("Youdim and Finberg 1986") (DTX 1076.) Youdim and Finberg 1986 explained that, of the various MAO inhibitors discovered, AGN 1135 was the most promising candidate for drug development because of its restricted resemblance to (-) deprenyl, its MAO-B selectivity and its tyramine antagonism. The authors further noted that AGN 1135 prevented MPTP-induced parkinsonism and that MAO-B inhibitors guarded against dopaminergic neuronal degeneration in Parkinson's disease patients. Youdim and Finberg 1986 stated that MAO-B inhibitors alone may prevent this neuronal degeneration. Youdim and Finberg 1986 taught that (-) deprenyl's effectiveness in the treatment of Parkinson's disease was not related to its unique intrinsic pharmacology, as other MAO-B inhibitors such as AGN 1135 share a similar pharmacological profile to (-) deprenyl. (DTX 1076 at 127, 134; Tr. 458:16-459:4.)

Finally, Youdim authored an article in 1986 entitled "Pharmacology of MAO B inhibitors: mode of action of (-) deprenyl in Parkinson's disease." ("Youdim 1986") (DTX 1075.) Similar to the prior art articles discussed above, Youdim 1986 taught that (-) deprenyl, which lacked the cheese effect, was useful as an adjunct to L-DOPA for the treatment for Parkinson's disease. Youdim 1986 also explained that AGN 1135 was a highly selective irreversible MAO-B inhibitor which was devoid of the cheese effect and shared similar biochemical and pharmacological properties to (-) deprenyl. Youdim 1986 further disclosed that

AGN 1135 had high selectivity for human and rat brain MAO-B as measured in vitro and in vivo and blocked the action of MPTP. (DTX 1075 at 96, 99-100; Tr. 136:18-137:8 (Youdim).)

In sum, these articles indicate that, as of the priority date of the '446 Patent, it was known that:

a. selective inhibitors of MAO-B had potential therapeutic value in the treatment of Parkinson's disease;

b. 80% of the MAO activity in the brain involves the MAO-B form of the enzyme;

c. (-) deprenyl was a selective MAO-B inhibitor that was useful as an adjunct to L-DOPA in the treatment of Parkinson's disease and that (-) deprenyl inhibited the tyramine pressor effect;

d. the clinical usefulness of (-) deprenyl derived from the fact that it was an MAO-B inhibitor;

e. Parkinson's disease patients treated with (-) deprenyl and L-DOPA had a significant prolongation of their life span compared to those patients treated with L-DOPA alone;

f. AGN 1135 showed biochemical and pharmacological properties similar to (-) deprenyl in that it was a potent, highly selective and irreversible inhibitor of MAO-B that did not cause tyramine potentiation;

g. AGN 1135 lacked (-) deprenyl's amphetamine-like actions; and

h. AGN 1135, like (-) deprenyl, protected against MPTP-induced parkinsonism.

(See DTX 1032 at 205, 206, 216; DTX 1033 at 346, 348, 353; DTX 1042 at 31, 34, 4; DTX 1034 at 65, 66, 70; DTX 1044 at 55, 60; DTX 1062 at 545; DTX 1066 at 313, 315, 316; DTX 1076 at 127, 134; DTX 1075 at 96, 99-100; DTX 1074 at 1364; DTX 5001 at 53.)

c. Potential Issues with AGN 1135

i. Preference for Reversible MAO-B Inhibitors

Despite the promise suggested by the prior art articles, Teva identified several potential issues in prior art that may have led a POSA away from investigating AGN 1135 as a potential treatment for Parkinson's disease. First, Teva presented testimony that it was a POSA's desire to develop a reversible MAO-B inhibitor rather than an irreversible inhibitor such as AGN 1135. (Tr. 686:9-15 (Jenner).)[11] Dr. Jenner explained that a reversible MAO-B inhibitor would have been preferred over an irreversible MAO-B inhibitor because when an individual is treated with a reversible enzyme inhibitor, the enzyme resumes functioning once the inhibitor compound is no longer administered. In contrast, with an irreversible inhibitor, the enzyme remains inactive even after the inhibitor compound is gone. As such, the body must synthesize more of the enzyme before enzyme function can resume. (Tr. 686:16-687:9 (Jenner).) According to Dr. Jenner, reversible MAO-B inhibitors would likely have been preferred because any adverse events, including but not limited to the potential cheese effect,[12] could be better managed by stopping the inhibitor. (Tr. 687:5-9 (Jenner); see also PTX 131.) Dr. Castagnoli admitted that

[11] Ro-19-6327 was one such reversible MAO-B inhibitor that was being investigated in the late 1980s. (Tr. 687:10-688:4 (Jenner); PTX 137; PTX 138; PTX 151.)

[12] Dr. Ruffolo testified that the risk of causing the cheese effect was viewed as a major impediment by the pharmaceutical industry in 1990 to the development of any MAO inhibitor compound. (Tr. 820:11-18 (Ruffolo).) However, the Court finds this argument only slightly probative with regard to AGN 1135, as it was known prior to 1990 that the cheese effect resulted from the inhibition of MAO-A. (DTX-1043 at 388.) As such, it was understood that selective MAO-B inhibitors did not cause the cheese effect. (DTX-1034 at 388.) More importantly, the prior art articles – the majority of which were authored by the inventors of the '446 Patent– indicated that AGN 1135 was specific to the MAO-B enzyme and therefore did not cause the cheese effect. (DTX 1032; DTX 1033; DTX 1034; DTX 1044; DTX 1062; DTX 1066; DTX 1076.)

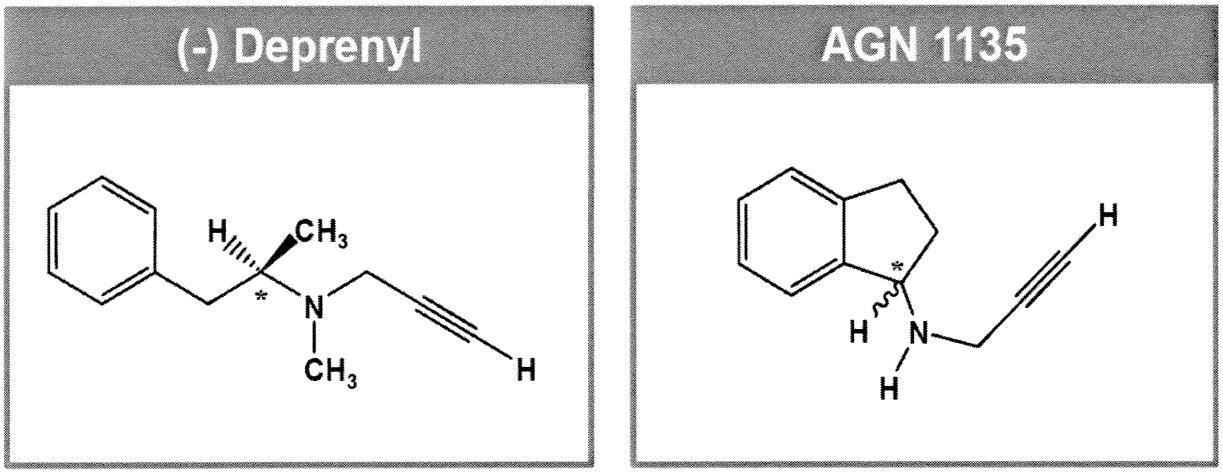
termination of an undesired effect was more easily achieved with a reversible drug than an irreversible one. (Tr. 408:16-18 (Castagnoli).) Similarly, an article co-authored by Dr. Castagnoli indicates that reversible MAO-B inhibitors would be safer than (-) deprenyl. (Tr. 409:17-410:6 (Castagnoli); PTX 219.)

ii. Lack of structural similarity to (-) deprenyl

Teva also highlighted at trial another potential issue with AGN 1135 – its structural dissimilarity to (-) deprenyl. Dr. Jenner presented evidence that there were known close structural analogs of (-) deprenyl that would have been more attractive MAO-B inhibitors than AGN 1135. (Tr. 689:9-690:2 (Jenner).) Specifically, Dr. Jenner provided information on two close structural analogs of (-) deprenyl – U-1424, and 4-fluorodeprenyl – that were reported in the prior art to have properties equivalent or superior to those of (-) deprenyl in several biochemical and pharmacological tests relevant to Parkinson's disease. (Tr. 692:11-693:25 (Jenner).) The compound U-1424 differs from (-) deprenyl only in that the six member phenyl ring on the left side of the (-) deprenyl molecule is replaced by a five member furanyl ring in U-1424. (Tr. 692:20-25 (Jenner).) Further, U-1424 was reported to be a promising selective MAO-B inhibitor. (Tr. 693:11-16 (Jenner).) Similarly, 4-fluorodeprenyl has the same structure as (-) deprenyl with the addition of a fluorine atom attached to the phenyl ring in the 4-position. (Tr. 693:1-4 (Jenner).) 4-fluorodeprenyl also showed increased dopamine levels in the brain and was reported to be efficacious in animal models of Parkinson's disease. (Tr. 693:17-25 (Jenner); PTX 185.)

On the other hand, aside from similarities in AGN 1135's and (-) deprenyl's mode of pharmacological action – i.e. both are MAO-B inhibitors – Dr. Ruffolo testified that a POSA

would not have considered AGN-1135 to be a close structural analog of (-) deprenyl. While the two molecules both have a propargylamine group (Tr. 1053:19-23 (Ruffolo)), Dr. Ruffolo testified that a POSA would recognize that there are other major structural differences between AGN-1135 and (-) deprenyl, including:



- the location of the respective chiral carbons in the two molecules. (Tr. 858:1-12 (Ruffolo).) In (-) deprenyl, the chiral carbon is located two positions away from the phenyl ring, while in AGN 1135 the chiral carbon is located one position away from the phenyl ring. (Id.)
- the ability of the respective chiral carbons to rotate in space. (Tr. 858:13-860:19 (Ruffolo).) While the chiral carbon in (-) deprenyl can adopt almost any position in space, the chiral carbon in AGN 1135 is fixed to the phenyl ring and is much more limited in its movement. (Id.)
- the ability of the groups of atoms attached to the chiral carbon to rotate in space. (Tr. 860:21-861:7 (Ruffolo).) While the three groups attached to the chiral carbon in (-)

deprenyl can rotate freely, only one group attached to the chiral carbon in AGN 1135 can rotate freely. (Id.)

- the environments surrounding the respective chiral carbons. (Tr. 861:8-862:6 (Ruffolo).) The chiral carbon in (-) deprenyl exists in a relatively free environment, with only one methyl group in close proximity, while the chiral carbon in AGN 1135 is surrounded by a bulky structure. (Id.)
- the number of groups attached to the nitrogen. The nitrogen attached to the chiral carbon in (-) deprenyl has three groups of atoms attached to it, rendering it a "tertiary amine," while the nitrogen attached to the chiral carbon in AGN 1135 has only two groups of atoms attached to it, rendering it a "secondary amine." (Tr. 862:9-24 (Ruffolo).)

Dr. Ruffolo explained that a POSA as of 1990 would have understood the importance of all of these structural differences between AGN 1135 and (-) deprenyl. (Tr. 862:25-863:2 (Ruffolo).) Dr. Castagnoli agreed that there are many structural differences between AGN 1135 and (-) deprenyl. (Tr. 434:19-437:1 (Castagnoli).)

F. Resolution of Racemic Mixtures

In addition to the compounds detailed above, several references related to the resolution of racemic compounds are also of importance in the scope of prior art. In particular, Mylan offered into evidence three prior art articles that were not cited by the patentees to the PTO during the prosecution of the '446 Patent: Ariens 1984 (DTX 1059); the FDA's 1987 Guidelines (DTX 1087); and DeCamp 1987 (DTX 1126). Although discussed in more detail below, it is important to note here that the parties additionally dispute whether there would have been a

reasonable expectation of success that the R(+) enantiomer of AGN 1135 would be an effective treatment for Parkinson's disease.

1. The Prior Art Articles on Resolution

In 1984, Dr. E.J. Ariens, an expert in stereochemistry, discussed in an article the importance of separating and evaluating enantiomers of racemic compounds (DTX 1059 at 663), explaining that "[o]ften only one isomer is therapeutically active, but this does not mean that the other is really inactive." As such, "[i[t may very well contribute to the side-effects" and therefore the "therapeutically non-active isomer in a racemate should be regarded as an impurity (50% or more)." (Id.) The Ariens article also stated that "[o]ne must be aware of the fact that stereoisomers definitely are different chemicals, mostly with quite distinct biological properties." (Id. at 664.)

The second reference regarding resolution of enantiomers is the FDA Guidelines for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances (the "Guidelines"), issued in February 1987. (DTX 1087.) The Guidelines instructed that "[w]hen the [New Drug Substance] is asymmetric (e.g., contains one or more chiral centers …), the sponsor should ideally (and prior to the submission of an IND) have either separated the various potential stereoisomers of the NDS or synthesized them independently." (Id.) The Guidelines further disclosed that "[p]hysical/chemical information about each stereoisomer should be provided (in detail), or may be requested." (Id.) Finally, "[i]ndividual stereoisomers may need to be studied for pharmacologic and toxicological properties (and/or for safety and efficacy)." (Id.)

Finally, the Wilson DeCamp article discussed the "current regulatory position of the [FDA] with regard to the approval of racemates and pure stereoisomers." (DTX 1126 at Abstract.) In particular, DeCamp wrote that "good science" requires that "enantiomers should be separated or they should be synthesized" as does "good sense." (DTX 1126 at 6.) DeCamp concluded that whenever a "drug can be obtained in a variety of chemically equivalent forms (such as enantiomers) it is both good science and good sense to explore the potential for in vivo differences between these forms." (DTX 1126 at 6.)

In responding to these articles, Dr. Ruffolo explained that a POSA prior to 1990 would have understood the statements in the Ariens article (DTX 1059) regarding enantiomers in a racemic compound to be part of an ongoing, unsettled discussion that was taking place at the time in the scientific community. (Tr. 836:5-16 (Ruffolo).) Dr. Ruffolo was personally involved in these discussions, which included members of the pharmaceutical industry, academic scientists, and the FDA. (Id.) Dr. Ruffolo testified that the discussion on whether drugs should be marketed as separated enantiomers or as racemic compounds was in a "state of flux," and that no firm conclusions about the desirability of enantiomer separation had been reached by 1990. (Id.)

Dr. Ruffolo also testified that the 1987 FDA Guidelines were concerned with the drug manufacturing process rather than the drug discovery process. (Tr. 835:4-13, 20-22 (Ruffolo).) As such, Dr. Ruffolo clarified that the Guidelines would likely not have been seen by POSAs working on drug discovery, where the decision on whether to separate a racemic compound is typically made. (Id.) Moreover, Dr. Ruffolo testified that the Guidelines did not provide any directive or mandate for the development of single enantiomer drugs. (Tr. 835:23-836:4

(Ruffolo).) Dr. Castagnoli conceded that the Guidelines were directed not to drug *development*, but to the drug *approval* process, which takes place "long after the drug [i]s discovered … long after all the pre-clinical testing [i]s done, and … the clinical trials [a]re completed." (Tr. 426:9-427:6 (Castagnoli).)

Finally, Dr. Ruffolo testified that the 1989 DeCamp article (DTX 1126) was adapted from a symposium presentation of an FDA employee and simply discussed the 1987 FDA Guidelines. (Tr. 837:2-7 (Ruffolo).) The DeCamp article also made clear that the decision to develop and market a racemic mixture versus a separated enantiomer "rests solely with the pharmaceutical company," and acknowledged that this decision is usually made some time before a drug company applies for FDA approval. (Tr. 837:8-14 (Ruffolo).)

2. Supposed Benefits of Enantiomer Separation

At trial, the parties presented conflicting evidence as to whether a POSA would have been interested in resolving AGN 1135 into its enantiomers. Dr. Castagnoli testified that a POSA would have known that the beneficial properties of AGN 1135 derive in whole or in part from one of the enantiomers of the racemic mixture and that the known properties of the mixture could be improved by resolution. (Id.) Dr. Castagnoli further emphasized that a POSA would have been motivated to separate the enantiomers of AGN 1135 because, as of January 3, 1990, a POSA would have understood that when the enantiomers of a racemic compound are resolved, there are three possibilities: (1) the racemate is the best drug candidate, (2) the R enantiomer is the best drug candidate, or (3) the S enantiomer is the best drug candidate. (Tr. 282:16-283:9 (Castagnoli).) However, Dr. Castagnoli admitted that he did not have significant involvement in

the development of treatments for Parkinson's disease in the late 1980s. (Tr. 383:3-6 (Castagnoli).)

Dr. Ruffolo, on the other hand, explained that in general, there is no way to predict based on the racemic compound whether a separated enantiomer will have any particular characteristic necessary to be a successful drug for treating Parkinson's disease or any other disease. (Tr. 842:20-25; 843:1-5 (Ruffolo). For example, one enantiomer may have a similar activity to the other enantiomer or to the racemate (Tr. 837:15-23; 840:12-20 (Ruffolo), each enantiomer could have completely different but complementary activities (Tr. 837:24-838:8 (Ruffolo)), or one enantiomer could have characteristics that would make it dangerous to administer to humans. (Tr. 838:19-22 (Ruffolo).) It is also possible for enantiomers to interact such that one enantiomer either enhances or blocks the activity of the other. (Tr. 843:1-12 (Ruffolo).) As such, until the enantiomers are separated and tested, there is no way to distinguish among these many possibilities. (Id.)

In support of his analysis, Dr. Ruffolo presented evidence on examples of drug compounds where, although one enantiomer may have been more active than the other, neither alone possessed all of the properties necessary to be a successful drug. (Tr. 837:24-838:8 (Ruffolo).) These drug compounds included dobutamine, carvedilol, and nebivolol. (Id.) Dr. Ruffolo also gave testimony on examples of compounds where each enantiomer had activity equal to that of the racemic compound. (Tr. 840:12-20 (Ruffolo).) These drug compounds included fluoxetine, warfarin, several antibiotics, antidepressants and non-steroidal anti-inflammatory agents. (Id.)

3. Reasonable Expectation of Success

Finally, Dr. Ruffolo testified that, in 1990, there was no basis for a reasonable expectation of success that the R(+) enantiomer of AGN 1135 would possess all of the properties needed to be a successful Parkinson's disease treatment. (828:15-21; 842:2-14 (Ruffolo).) First, Dr. Ruffolo explained that the facts known about AGN 1135 in 1990 – i.e. that it was a potent, selective and irreversible MAO-B inhibitor that was not metabolized to amphetamines, that it did not potentiate the tyramine pressor effect in animals, and that it was effective in the MPTP mouse model (Tr. 840:24-841:6 (Ruffolo)) – were insufficient to provide a reasonable expectation of success that AGN-1135 *itself* would be effective in treating Parkinson's disease. (Tr. 841:7-12 (Ruffolo).) In fact, all three experts testified that there was no description in the prior art of the actual use of AGN 1135 to treat Parkinson's disease. (Tr. 411:23-412:1 (Castagnoli); 605:22-606:5 (LeWitt); 841:13-16 (Ruffolo).)

Second, Dr. Ruffolo attested, and Dr. Castagnoli admitted, that there was no description in the prior art of any separation, isolation, or characterization of the enantiomers of AGN 1135. (Tr. 417:3-7 (Castagnoli); 841:23-842:1 (Ruffolo). As such, the properties of R(+)-PAI, including any MAO-B inhibitory activity, were unknown. (Tr. 842:2-4 (Ruffolo); Tr. 842:5-9; 843:13-19 (Ruffolo).) Similarly, there was no prior description about the tyramine pressor effect of the enantiomers of AGN 1135 because the enantiomers of AGN 1135 did not exist in the prior art. (Id.) Finally, as of 1990, there was no information on whether either enantiomer of AGN 1135 would possess all of the additional favorable characteristics of R(+)-PAI, including the appropriate absorption, distribution, metabolism, and elimination ("ADME") characteristics required to be an effective treatment for Parkinson's disease. (Tr. 842:10-14 (Ruffolo).)

III. Level of Ordinary Skill in the Art

The parties' proposed definitions of the level of skill in the art are substantially similar. (Compare SOF ¶ 124 with ¶ 1212.) Essentially, Teva and Mylan agree that a POSA is someone who, as of January 3, 1990 would have had a Ph.D. in pharmacology, medicinal chemistry, or a related discipline, and several years of experience in drug discovery research, which would include knowledge about the different classes of drugs that were known or being investigated for treating Parkinson's disease. (TPFF ¶ 115.) A POSA would also have knowledge of stereochemistry, including knowledge regarding the resolution of racemates into their enantiomers. (Id.) The only material difference between the parties' proposals is that Mylan's definition also includes a person having a "medical degree" who would "have access to individuals with expertise in biochemistry, molecular biology, and pharmacology." (MPFF ¶ 89.) Given that this case involves a method of treatment claim, the Court agrees with Mylan that a POSA could also include a person with a medical degree with access to individuals with expertise in biochemistry, molecular biology, and pharmacology. Mayo Collaborative Serv. v. Prometheus Labs., Inc., 132 S. Ct. 1289, 1297 (2012) (explaining that in a method claim, "the 'administering' step simply refers to the relevant audience, namely doctors who treat patients with certain diseases").

IV. Differences between the Claimed Subject Matter and the Prior Art

A. Lead Compound Analysis

Before turning to the differences between the claimed subject matter and the prior art, the Court must first address the parties' dispute regarding whether a "lead compound analysis" should be utilized in the obviousness inquiry.

Traditionally, a lead compound analysis is applied when the claims of a patent are directed to a new chemical compound. See, e.g., Eisai Co. v. Dr. Reddy's Labs., Ltd., 533 F.3d 1353, 1359 (Fed. Cir. 2008) (explaining that "post-KSR, a prima facie case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound" in the prior art); Unigene Labs., Inc. v. Apotex, Inc., 655 F.3d 1352, 1361 (Fed. Cir. 2011) ("Where the patent at issue claims a chemical compound, a lead compound is often used to show structural similarities between the claimed compound and prior art.").

Teva points to several cases in which courts have applied a lead compound analysis to a patent that includes a method claim. However, all of the cases cited by Teva involved claims related to new chemical compounds *in addition to* claims involving methods of using such compounds. As such, the district courts in these cases would necessarily apply a lead compound analysis to the claims involving a new chemical compound. For example, in Otsuka Pharm. Co. v. Sandoz, Inc., 678 F.3d 1280 (Fed. Cir. 2012), the Federal Circuit affirmed the district court's application of a lead compound analysis to – and its finding of validity of – a patent claiming the new chemical compound aripiprazole. After upholding the validity of the compound claim, the Federal Circuit further explained that it need not review the validity finding on the dependent method claim. Id. at 1296. As such, the Federal Circuit did not employ a lead compound analysis on a method of treatment claim, but rather affirmed the district court's traditional use of a lead compound analysis on a new chemical compound claim. See also P&G v. Teva Pharms. USA, Inc., 566 F.3d 989 (Fed. Cir. 2009) (applying a lead compound analysis to a patent that claimed the compound risedronate, pharmaceutical compositions containing risedronate *and* methods of treating diseases using risedronate); Novartis Pharms. Corp. v. Roxane Labs., Inc.,

No. 08-cv-3853 2011 U.S. Dist. LEXIS 35545, at *3, *12-15 (D.N.J. Mar. 31, 2011) (applying a lead compound analysis to a patent claiming both a chemical compound *and* a method of use of that compound); Merck Sharp & Dohme Pharms. v. Teva Pharms. USA, Inc., No. 07-1596, 2009 U.S. Dist. LEXIS 131869, at *136-142 (D.N.J. Aug. 19, 2009) (same); Janssen Pharmaceutica N.V. v. Mylan Pharms., Inc., 456 F. Supp. 2d 644, 656-657 (D.N.J. 2006) (same).

In sum, Teva points to no case in which a lead compound analysis is applied to a patent that contains *only* a method of treatment claim without a corresponding claim to a compound itself. In any event, whether or not a lead compound analysis is considered, the ultimate question here, is whether it would have been obvious to a POSA in 1990 to treat Parkinson's disease by administering to a patient the MAO-B inhibitor R(+)-PAI. The Court finds that it would not have been obvious to do so because, for many of the reasons set forth above, this Court finds that the differences between the prior art and the invention covered by the '446 Patent are significant.

B. Differences Between the Prior Art and the Claimed Invention

First, this Court finds that the prior art was not in accord as to the promise of either AGN 1135 or R(+)-PAI as the most attractive candidate for a Parkinson's disease drug based on the presence of several *other* promising candidates, including dopamine agonists, COMT inhibitors and L-DOPA pro-drugs. When the prior art as a whole is considered, only hindsight bias could support the conclusion that R(+)-PAI would have been selected as a potential treatment for Parkinson's disease. See Eli Lilly & Co. v. Zenith Goldline Pharms., Inc., 471 F.3d 1369, 1379 (Fed. Cir. 2006) ("[M]ere identification in the prior art of each component of a composition does not show that the combination as a whole lacks the necessary attributes for patentability, i.e. is obvious."); see also KSR, 550 U.S. at 421 (cautioning against "the distortion caused by hindsight

bias" and "arguments reliant upon ex post reasoning" in determining obviousness); Processing Corp. v. Am. Maize-Products Co., 840 F.2d 902, 907 (Fed. Cir. 1988) (noting that in considering obviousness, "[c]are must be taken to avoid hindsight reconstruction by using the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit") (internal citations omitted). Having considered the prior art as a whole—and being mindful of the complexities of Parkinson's disease, the causes of which remain unknown to this day—the Court does not find that a POSA in 1990 would have selected R(+)PAI as a treatment for Parkinson's disease over *all* of the other potential drug candidates.

Second, the relevant prior art patents that discuss and/or claim AGN 1135 – the '037 Patent and the '244 Patent – did not describe AGN 1135 as an inhibitor of the B form of MAO, did not describe the separation or characterization of the enantiomers of AGN 1135, and most importantly, did not disclose AGN 1135 as a potential treatment for Parkinson's disease. Without such knowledge, there would have been no basis from the prior art patents to draw a conclusion about the use of AGN 1135 to treat Parkinson's disease. (Tr. 814:5-8 (Ruffolo).) In fact, the marked blood pressure lowering effect described in the '244 Patent may have discouraged a POSA from choosing AGN 1135 as a potential new treatment for Parkinson's patients, who are known to suffer from orthostatic hypotension.

Third, despite the promising information regarding MAO-B inhibitors in the prior art articles, there were several issues associated with the use of AGN 1135 to treat Parkinson's disease. For example, Teva presented evidence that a POSA would likely have selected a reversible MAO-B inhibitor over an irreversible one, which would allow for a more easy

termination of undesired drug effects. In addition, Mylan did not present sufficient expert testimony to persuasively rebut Dr. Jenner's and Dr. Ruffolo's testimony that a POSA would have chosen a close structural analog of (-) deprenyl, rather than AGN 1135, in the hopes of improving upon (-) deprenyl's effectiveness as a treatment for Parkinson's disease. In other words, Teva's experts presented cogent evidence that the significant structural differences between AGN 1135 and (-) deprenyl would have made AGN 1135 a less obvious candidate as a potential treatment for Parkinson's disease. Finally, although the DATATOP study sparked interest in (-) deprenyl as a monotherapy and in the potential neuroprotective effects of MAO-B inhibitors, Dr. LeWitt admitted that he did not have any direct evidence that the results of the DATATOP study created any increased interest in AGN 1135, in particular, before January 2, 1990. (Tr. 614:24-615:3 (LeWitt).)[13]

Fourth, the prior art regarding the desirability of enantiomer separation was unsettled at best in 1990, and the relevant prior art articles do not provide clear and convincing evidence that the separation of AGN 1135 was obvious to try. See Sanofi-Synthelabo v. Apotex, Inc., 550 F.3d 1075 (Fed. Cir. 2008) (explaining that general knowledge in the field of stereochemistry "confirms, that the recognition that stereoisomers may exhibit different properties does not teach which results may ensue or how to separate any given enantiomers"). This is especially true given that, at that time, the FDA did not mandate that racemic compounds be resolved into their enantiomers, but merely provided manufacturing guidelines for the drug approval process.

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[13] That the conclusions in the DATATOP study were eventually discovered to be somewhat inaccurate (Tr. 614:19-22 (LeWitt)) has no bearing on what a POSA would have understood regarding the study in 1990.

Moreover, the fact that the resolution of a racemic compound could lead to any number of possible outcomes in terms of both efficacy and safety would not necessarily have motivated a POSA to separate AGN 1135 based on a general expectation that one enantiomer would be more active than the other. "A new composition is 'obvious to try' when it is reasonable to expect that the trial will produce a predictable result." Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd., No. 2011-1223, 2013 U.S. App. LEXIS 12251, at *37 (Fed. Cir. June 18, 2013); see also KSR, 550 U.S. 398, 421, (2007) (explaining that "the fact that a combination was obvious to try might show that it was obvious under § 103" if, among other things, "there are a finite number of identified, predictable solutions").

As explained by Dr. Ruffolo, that situation did not exist in 1990 with regard to the separation of AGN 1135. See Eisai Co. v. Dr. Reddy's Labs., Ltd., 533 F.3d 1353, 1359 (Fed. Cir. 2008) ("To the extent an art is unpredictable, as the chemical arts often are, KSR's focus on these 'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable."). Mylan did not adequately rebut Teva's expert testimony that there was no basis for a reasonable expectation of success that R(+)-PAI would have any of the properties required to be an effective treatment for Parkinson's disease, let alone *all* of them. (Tr. 843:1-12 (Ruffolo).)[14] Sanofi-Synthelabo v. Apotex, Inc., 550 F.3d 1075 (Fed.

[14] The Court finds Teva's additional arguments regarding the increased cost of manufacturing based on the separation of enantiomers and the issues involved with separating enantiomers on a production scale to be less persuasive. (See TPFF ¶¶ 249, 257.) This is because "[t]here is no requirement that one of ordinary skill have a reasonable expectation of success in developing [the commercial product]. Rather, the person of ordinary skill need only have a reasonable expectation of success of developing the *claimed invention*." Allergan, Inc. v. Sandoz Inc., Nos. 2011-1619, -1639, -1620, -1635, 2013 U.S. App. LEXIS 8837, at *6 (Fed. Cir. May 1, 2013) (emphasis added).

Cir. 2008) (finding the patent not obvious because there was no reasonable expectation of success that claimed enantiomer would manifest all of the relevant properties and advantages). Indeed, Mylan provided no evidence that anyone had ever attempted to separate the enantiomers of AGN 1135 between the disclosure of AGN 1135 in the '037 Patent in 1966 and the priority date of the patent in January 1990.

In view of this Court's findings with respect to the first three Graham Factors, this Court finds that Mylan has not established, by clear and convincing evidence, that the '446 Patent is invalid for obviousness.

One case cited by Mylan in support of its obviousness argument, Aventis Pharma Deutschland GMBH v. Lupin Ltd., 499 F.3d 1293 (Fed. Cir. 2007), requires further discussion. The patent at issue in Aventis was directed to the pharmaceutical compound ramipril – in the form SSSSS – "substantially free of other isomers." Id. at 1295. Following a trial, the district court held that the defendant failed to establish by clear and convincing evidence that a POSA would have been motivated to purify SSSSS ramipril into a composition substantially free of other isomers. Id. at 1300.

The Federal Circuit reversed based on the existence of two prior art compounds. The first contained a mixture of SSSSS ramipril together with its SSSSR stereoisomer. Id. at 1300. The second, a well-known prior art molecule named enalapril, shared a close structural analogy with ramipril. Id. at 1302. The Federal Circuit explained that the prior art compounds provided a sufficient motivation to purify SSSSS ramipril as the therapeutic stereoisomer because "[i]n enalapril, . . .all of the stereocenters are in the S configuration" and the prior art "taught that the SSS configuration of enalapril is 700 times as potent as the SSR form." Id. As such, the "close

structural analogy between . . . ramipril and . . . enalapril would have led a person of ordinary skill to expect" that SSSSS ramipril would be the more potent enantiomer. Id.

Here, the closest prior art compound, (-) deprenyl, does *not* share a close structural similarity with R(+)-PAI. In brief, the chiral carbons are at different locations; the chiral carbon in (-) deprenyl is free to rotate while on AGN 1135, it is anchored in a rigid ring structure; the three groups attached to the chiral carbon in (-) deprenyl rotate while only one group rotates in AGN 1135; the environmental bulk around the chiral carbon in AGN 1135 is much greater; and the groups attached to the nitrogen in AGN 1135 differ. Therefore, unlike the situation with the structurally similar compounds at issue in Aventis, a POSA in 1990 would not have expected the R-form of AGN 1135 to be the active enantiomer based on a structural similarity to (-) deprenyl.

More relevant to this Court's analysis is Sanofi-Synthelabo v. Apotex, Inc., 550 F.3d 1075 (Fed. Cir. 2008). There, the patent claimed the compound Clopidogrel, the dextrorotatory (+) isomer of the chemical compound methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thienopyridyl)(2-chlorophenyl) -acetate. Id. at 1077. The Federal Circuit's analysis focused on the patentability of this dextrorotatory isomer in view of its known racemate, which was fully described in earlier patents. Id. at 1078. On the basis of this trial evidence, the district court found that a POSA would not have reasonably predicted that the dextrorotatory enantiomer would provide all of the required therapeutic activity with none of the adverse neurotoxicity. Id. at 1087. The district court further found that separation of the enantiomers was not a simple or routine procedure and that success in separation, as well as the allocation of properties, was unpredictable. Id. at 1088.

The Federal Circuit affirmed. Specifically, the Federal Circuit explained that "[o]nly with hindsight knowledge that the dextrorotatory enantiomer has highly desirable properties"

could the defendant argue that "it would have been obvious to select this particular racemate and undertake its arduous separation." Id. at 1088. Similar to this case, the Federal Circuit found the "application of hindsight . . . inappropriate where the prior art d[id] not suggest that th[e] enantiomer could reasonably be expected to manifest the properties and advantages that were found for this particular dextrorotatory isomer." Id.

In sum, for the reasons stated above, the Court finds that Claim 1 of the '446 Patent is not invalid as obvious over the prior art. Because Claims 2, 17, 18 and 19 are dependent claims, the Court need not conduct a separate obviousness analysis for these claims. See Synqor, Inc. v. Artesyn Techs., inc., 709 F.3d 1365 (Fed. Cir. 2013) ("This court need not consider Defendants' arguments that certain dependent claim limitations would have been obvious where the base claim has not been proven invalid.").

In arriving at this conclusion, the Court found both Mylan's and Teva's experts to be credible and qualified. This Court's independent consideration of the totality of the prior art, however – after having the benefit of the experts' opinions – aligns more closely with the view of Dr. Jenner and Dr. Ruffolo.

V. Secondary Considerations

As Mylan has failed to demonstrate obviousness in accordance with the initial Graham factors, the Court need not consider the objective indicia of nonobviousness. See Takeda Chem. Indus. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1363 (Fed. Cir. 2007) ("In light of our conclusion that [the patent challenger] failed to prove that the claimed compounds would have been prima facie obvious, we need not consider any objective indicia of nonobviousness.").

However, the Court notes that the relevant secondary considerations do in fact support the Court's finding of nonobviousness.

"[S]econdary considerations [such] 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" and "may have relevancy" as indicia of obviousness or nonobviousness. AstraZeneca LP v. Breath Ltd., No. 08-1512, 2013 U.S. Dist. LEXIS 49375, at *75 (D.N.J. Apr. 1, 2013) (citing to Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966). Specifically, the Court finds persuasive Teva's evidence showing the failure of others, skepticism in the industry, the satisfaction of a long felt need, and the commercial success of Azilect®.

A. Failure of others

Teva presented evidence that several attempts by others to develop a treatment for Parkinson's disease were unsuccessful. Failure of others to "find a solution to the problem which the patent[] in question purport[s] to solve," can suggest that the inventor made a genuinely innovative discovery. Symbol Techs., Inc. v. Opticon, Inc., 935 F.2d 1569, 1578 (Fed. Cir. 1991). Dr. Ruffolo testified that some of these failures were due to lack of efficacy, some to safety concerns, and some to tolerability and a range of other problems. (Tr. 879:4-9 (Ruffolo).) The failed treatments included: the dopamine agonist ciladopa (failed because it produced testicular tumors in animals) (Tr. 879:18-20 (Ruffolo)); dopamine agonist CY-208-243 (failed because it did not produce any effect at low doses and produced toxicities in animals that prevented the study of increased doses in humans) (Tr. 879:21-24 (Ruffolo)); dopamine agonist lergotrile (failed because it produced liver toxicity and mental changes in humans) (Tr. 879:25-

880:2 (Ruffolo)); dopamine agonist mesulergine (failed because it produced tissue abnormalities in animals) (Tr. 880:3-4 (Ruffolo)); dopamine agonist CQA 206-291 (failed because it produced unacceptable blood test toxicity results in humans) (Tr. 880:9-11 (Ruffolo)); dopamine autoreceptor ligand (-) 3-PPP (failed because it produced inconsistent and weak results in humans) (Tr. 880:12-14 (Ruffolo)); MAO-B inhibitor MDL-72145 (failed because it produced anemia) (Tr. 879:15-17 (Ruffolo)); MAO-B inhibitor milacemide (failed because it increased the severity of Parkinson's disease symptoms in subjects) (Tr. 880:5-8 (Ruffolo)); and MAO-B inhibitor lazabemide (failed because it produced liver toxicity in humans). (Tr. 880:15-16 (Ruffolo); PTX 36.)

Additionally, some of the compounds intended for use in the treatment of Parkinson's disease failed after the development stage, after the drug had already been approved for marketing. (Tr. 880:17-23 (Ruffolo).) For example, after the approval and marketing of the COMT inhibitor tolcapone, patients taking this compound experienced liver toxicities and even death. (Tr. 880:24-881:13 (Ruffolo).) Tolcapone was withdrawn from the market in Europe and Canada and given a "black box" warning on its labeling in the U.S. (Id.) Similarly, pergolide, a dopamine agonist used in the treatment of Parkinson's disease, was subsequently withdrawn from the market because it produced valvular heart lesions. (Tr. 881:14-18 (Ruffolo).) As such, the apparent failure of others to create a safe and therapeutically effective treatment for Parkinson's disease supports a finding that Teva's accomplishment would not have been obvious to those skilled in the art.

B. Skepticism

Similar to failure of others, if contemporaneous observers expressed skepticism that the inventor's solution would solve the problem, this too can suggest nonobviousness. Tyco Healthcare Group LP v. Mutual Pharm. Co., Inc., 642 F.3d 1370, 1377 (Fed. Cir. 2011). One of the inventors listed on the '446 Patent, Dr. Moussa Youdim, testified that during the late 1970s and the first half of the 1980s, he attempted unsuccessfully to interest several pharmaceutical companies in the development of AGN 1135 as a possible treatment for Parkinson's disease. (Tr. 96:19-23 (Youdim); see also TPFF ¶¶ 82-89.) Dr. Youdim also testified that the inventors of the '446 Patent attended international meetings and congresses on Parkinson's disease, MAO inhibitors, and movement disorders. There, they presented data on AGN 1135 and attempted to interest other academic researchers in its development as a possible treatment for Parkinson's disease. (Tr. 102:17-102:24 (Youdim).) However, none of these conversations proved fruitful. (Tr. 102:25-103:3 (Youdim).) Finally, despite the numerous publications by Professors Youdim and Finberg on AGN 1135 discussed in detail above, the inventors were unsuccessful in interesting academic researchers in the further investigation of AGN 1135. (Tr. 102:25-103:3; 104:1-4 (Youdim).)

The Court does note that, aside from Dr. Youdim's testimony, there is only one letter in the record evidencing the communications between Dr. Youdim and these pharmaceutical companies. This letter from Warner Lambert, which is written in response to a proposal from Dr. Youdim for the development of AGN 1135, suggests that concerns over funding may have played a role in the company's rejection of Dr. Youdim's proposal. (See PTX 140.) In addition, the '037 Patent and the '244 Patent may have additionally dissuaded these pharmaceutical

companies from pursuing a compound that was already patented, albeit for another purpose. In any event, the Court finds that the overall skepticism shown by others in the pharmaceutical field about developing AGN 1135 as a treatment for Parkinson's disease supports a finding of nonobviousness. Indeed, the Court finds probative the fact that no MAO-B inhibitor other than (-) deprenyl was approved by the FDA to treat Parkinson's disease until Azilect® was approved in 2006. (Tr. 449:13-450:6 (Castagnoli).)

C. Satisfaction of a long felt need

"Evidence that an invention satisfied a long-felt and unmet need that existed on the patent's filing date is a secondary consideration of nonobviousness." Perfect Web Techs., Inc. v. Infousa, Inc., 587 F.3d 1324, 1332 (Fed. Cir. 2009). Teva provided testimony from Dr. Henchcliffe that, as of January 2, 1990, there remained a long-felt need for a safe, effective, and more tolerable drug that could be used as monotherapy to treat the symptoms of Parkinson's disease and delay the need for treatment with L-DOPA. (Tr. 1139:9-1140:19 (Henchcliffe).)[i] Specifically, the 2002 TEMPO study demonstrated that Azilect®, when given as once-daily monotherapy, was effective and improved a range of scores on the Unified Parkinson's Disease Rating Scale, including improvements in motor function, activities of daily living, and amelioration of tremor and bradykinesia. (Tr. 1130:8-1134:11 (Henchcliffe); PTX 98.) The TEMPO study also demonstrated that use of Azilect® as monotherapy improved patients' quality of life based on feedback from patients on the drug. (Id.)

Finally, Dr. Henchcliffe presented evidence that Azilect® may slow the clinical progression of Parkinson's disease. (Tr. 1144:8-1149:19 (Henchcliffe); PTX 109; PTX 96.) In 2009, Teva completed the ADAGIO clinical trial, a large study involving almost 1200 patients

with early Parkinson's disease in 130 centers throughout the world. (Tr. 1145:12-1147:15 (Henchcliffe); PTX 96.) Although the study produced mixed results, the outcomes indicated that the currently marketed 1 mg dose of Azilect® produced a disease-modifying benefit. (Tr. 1147:16-1149:19 (Henchcliffe); PTX 96.) This conclusion is further supported by preclinical studies in animals suggesting that rasagiline has neuroprotective properties. (Tr. 1144:13-1145:14 (Henchcliffe); PTX 109.) Based on this data, Dr. Henchcliffe opined that "more likely than not," Azilect® slows the clinical progression of Parkinson's disease, (Tr. 1144:8-12; 1181:3-18 (Henchcliffe)), notwithstanding the FDA's rejection of a change in the Azilect® labeling to include a modification of the clinical progression of the disease (DTX 1444). In fact, Dr. LeWitt acknowledged that there is a "large body of basic science data" suggesting that Azilect® has the potential to be neuroprotective. (Tr. 561:11-562:7 (LeWitt).) Thus, there is sufficient evidence to show that Azilect® satisfied a long-felt need for a Parkinson's disease drug that could be used as monotherapy and that could potentially slow the clinical progression of the disease.

D. Commercial success

Finally, Teva presented evidence on the commercial success of Azilect®. (Tr. 1213:12-20; 1213:24-1214:25; 1215:6-12; 1215:20-1216:19 (Hausman); PTX 659; PTX 744; PTX 749; PTX 750.) "Commercial success is relevant because the law presumes an idea would successfully have been brought to market sooner, in response to market forces, had the idea been obvious to persons skilled in the art. Thus, the law deems evidence of (1) commercial success, and (2) some causal relation or nexus between an invention and commercial success of a product

embodying that invention, probative of whether an invention was non-obvious." Merck & Co., v. Teva Pharms. USA, Inc., 395 F.3d 1364, 1376 (Fed. Cir. 2005) (citation & quotation omitted).

Dr. Hausman presented evidence that Azilect®'s cumulative worldwide sales since its launch through the end of 2012 totaled near $1.7 billion and its current annual worldwide sales are close to $500 million. (Tr. 1213:22-1214:12 (Hausman); PTX 659; PTX 744; PTX 749.) Further, Azilect®'s cumulative U.S. sales since its launch through the end of 2012 totaled over $650 million and its current annual U.S. sales are approximately $168 million. (Tr. 1215:19-1216:19 (Hausman); PTX 659; PTX 744; PTX 750.) Prescriptions for Azilect® have also steadily grown, starting from zero at the time of its launch to more than 100,000 per quarter in the United States as of 2012. (Tr. 1217:25-1218:19 (Hausman); PTX 198; PTX 748; PTX 751.) Cumulative U.S. prescriptions for Azilect® since the time of its launch total 1.7 million. (Id.)

Finally, Azilect® is the number one treatment in the market by revenue share, with a share of approximately 27%. (Tr. 1219:20-1220:19 (Hausman); PTX 197; PTX 748; PTX 752.) Azilect® also has the largest share of prescriptions among branded treatments for Parkinson's disease. (Tr. 1221:8-1222:19 (Hausman); PTX 198; PTX 748; PTX 753.) In fact, Azilect® has taken prescription share away from generic selegiline, with selegiline's prescription share decreasing with the growth of Azilect®'s, despite Azilect®'s higher price. (Tr. 1222:22-1223:14 (Hausman); PTX 198; PTX 748; PTX 753.) Dr. Hausman explained that Azilect®'s share of the market is particularly impressive given that it was launched after most of its competitors. (Tr. 1221:14-1223:18; 1224:16-1225:24 (Hausman). This is because early entrants into a pharmaceutical market typically enjoy a "first mover advantage" against therapies that are introduced later. (Id.)

The Court finds that Azilect®'s commercial success has a nexus to the invention of the '446 Patent. Azilect® is the commercial embodiment of the '446 Patent, which claims the use of rasagiline to treat Parkinson's disease as both monotherapy and adjunct therapy to L-DOPA. (Tr. 1228:10-1230:18 (Hausman); PTX 1; PTX 2.) Dr. Henchcliffe testified that physicians prescribe Azilect® because of its clinical benefits, all of which are inherent attributes of the claimed invention. (Tr. 1150:1-1150:13 (Henchcliffe); 1230:9-1233:8 (Hausman).) These include, but are not limited to, Azilect®'s efficacy, safety and tolerability. (Id.)

Mylan argues that the commercial success of the patented invention may stem from other patents in the same family as the '446 Patent. (See MPFF ¶¶ 283-287.) However, the fact that certain features of Azilect® may be covered by other patents from the same family as the '446 Patent does not negate the nexus between Azilect®'s commercial success and the '446 Patent. (Tr. 1248:12-22 (Hausman).) First, the '446 Patent is the only patent in that family that claims the use of R(+)PAI for treatment of Parkinson's disease as both monotherapy and adjunct therapy. Second, even if other patents in the family claim certain characteristics of Azilect® that contribute to its commercial success, there is no reliable way in this case to distinguish the contribution of one patent over another. (Tr. 1252:20-1253:16 (Hausman).) In other words, Mylan has not definitively shown that the claimed properties attributable to the other patents are responsible for Azilect®'s commercial success. This is important because a "patentee is not required to prove as part of its prima facie case that the commercial success of the patented invention is *not* due to factors other than the patented invention." Demaco Corp. v. F. Von Langsdorff Licensing, Ltd., 851 F.2d 1387, 1311 (Fed. Cir. 1988) (emphasis added). "It is sufficient to show that the commercial success was of the patented invention itself," because a

"requirement for proof of the negative of all imaginable contributing factors would be unfairly burdensome, and contrary to the ordinary rules of evidence." Id. See also Crocs, Inc. v. ITC, 598 F.3d 1294, 1311 (Fed. Cir. 2010) (explaining that once the patentee demonstrates a prima facie nexus, the burden of coming forward with evidence in rebuttal shifts to the challenger). As such, the Court finds that the commercial success of Azilect® supports a finding of nonobviousness.[15]

In sum, the Court finds that based on the four Graham factors, Claims 1, 2, 17, 18 and 19 of the '446 Patent are not invalid for obviousness.

ENABLEMENT

Mylan also argues that the '446 Patent does not provide an enabling disclosure under 35 U.S.C. § 112, ¶ 1, because the specification discloses only animal and in vitro testing information similar to that found in the prior art. (See MPFF ¶¶ 332-368.) Although Mylan did not present expert testimony on the matter,[16] Mylan argues that because the specification does *not* include clinical or human data – including but not limited to data related to selectivity against other targets, ADME information, and information on molecular synthesis (Tr. 818:13-819:8, 827:11-829:2, 843:22-852:1 (Ruffolo)) – the patent does not enable a POSA to use R(+)-PAI as a Parkinson's disease treatment.

A patent must enable one of skill in the art to make and use what is claimed. 35 U.S.C. § 112 ("The specification shall contain a written description of the invention, and of the manner

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[15] Teva's trial experts did not emphasize unexpected results, industry praise or copying. (TPFF ¶¶ 357-382.) Regardless, Teva has produced sufficient evidence on the other objective indicia of nonobviousness to support this Court's overall finding of nonobviousness.

[16] Neither Dr. Castagnoli nor Dr. LeWitt offered any opinion at trial with respect to the issue of

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."). The Federal Circuit has explained that enablement is a requirement distinct from that of written description. Ariad Pharms., Inc. v. Eli Lilly & Co., 598 F.3d 1336 (Fed. Cir. 2010). A patent is enabled when a POSA, having read the specification, can practice the invention without "undue experimentation." In re Wands, 858 F.2d 731, 736-37 (Fed. Cir. 1988). However, routine or standard experimentation is not "undue." Id.

Enablement is closely related to the requirement for utility. The utility requirement is defined in 35 U.S.C. § 101 as follows: "[w]hoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title." In essence, the utility requirement prevents the patenting of mere ideas. This is important because "[p]atent 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). Moreover, "the utility requirement also prevents the patenting of a mere research proposal or an invention that is simply an object of research." Janssen Pharmaceutica N.V. v. Teva Pharms. USA, Inc. (In re '318 Patent Infringement Litig.), 583 F.3d 1317, 1323-24 (Fed. Cir. 2009).

The Federal Circuit explained in Process Control Corp. v. HydReclaim Corp., 190 F.3d 1350, 1358 (Fed. Cir. 1999) that "the enablement requirement of 35 U.S.C. § 112, ¶ 1 requires

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enablement.

that the specification adequately discloses to one skilled in the relevant art how to make, or in the case of a process, how to carry out, the claimed invention without undue experimentation," while "[t]he utility requirement of 35 U.S.C. § 101 mandates that any patentable invention be useful and, accordingly, the subject matter of the claim must be operable." As such, "[i]f a patent claim 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." Id.

Mylan has failed to prove, by clear and convincing evidence, that the claims of the '446 Patent are invalid for lack of enablement and/or utility. The Federal Circuit has held that "human trials are not required for a therapeutic invention to be patentable." Janssen, 583 F.3d at 1324 (Fed. Cir. 2009). The Federal Circuit further explained that "patent applications need not 'prove that compounds or other materials which [the applicant] is claiming, and which [the applicant] has stated are useful for "pharmaceutical applications" are safe, effective, and reliable for use with humans.'" Id. (citations omitted). This is because if "Phase II testing [human trials]" were required "in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue . . . potential cures." Id. (citation omitted). As such, "results from animal tests or in vitro experiments may be sufficient to satisfy the utility requirement." Id. at 1325-25. See also In re Krimmel, 292 F.2d 948, 953 (C.C.P.A. 1961) (holding that animal tests showing that a new nonobvious compound "exhibits some useful pharmaceutical property" are sufficient to demonstrate utility); Cross v. Iizuka, 753 F.2d 1040, 1050-51 (Fed. Cir. 1985) (concluding that in vitro test results for a claimed pharmaceutical compound, combined with animal test results for a structurally similar compound, showed "a reasonable correlation between the

disclosed in vitro utility and an in vivo activity").

Here, the '446 Patent discloses both in vitro and in vivo data demonstrating that R(+)-PAI is a potent and selective MAO-B inhibitor. (PTX 1 at 11:61-12:1; 13:16-30; 14: 6-12; 14: 26-31; 15:51-17:2 (Example 24).) The specification explains that (-) deprenyl, like R(+)-PAI, belongs to the class of compounds known as MAO-B inhibitors and treats the symptoms of Parkinson's disease when used as adjunct therapy to L-DOPA. (PTX 1 at 1:66-2:3; 2: 31-37.) Finally, Example 25 of the '446 Patent discloses animal model data demonstrating that the MAO-B inhibitory activity of R(+)-PAI increases dopamine in the brain and influences motor control activity. (PTX 1, Example 25.)[17]

Based on the in vitro and in vivo information contained in the patent, Dr. Ruffolo testified that a POSA would have understood R(+)-PAI to be a potent and selective MAO-B inhibitor. (Tr. 885:8-16 (Ruffolo).) With regard to Example 25 in particular, Dr. Ruffolo explained that a POSA would have understood the test to represent a "standard and common" animal model used to measure a drug's ability to increase dopamine activity in the brain, a desired outcome in the treatment of Parkinson's disease. (Tr. 885:17-22 (Ruffolo).) Because R(+)-PAI increased the stereotyped head movements of the tested animals (Tr. 886:15-19 (Ruffolo)), a POSA would have concluded that R(+)-PAI, through inhibition of MAO-B, could potentially increase dopamine in the brain and therefore have a positive effect on motor activity

[17] To test a drug using the "potentiation of amphetamine-induced stereotyped behavior" model of Example 25, amphetamine is given to an animal. This causes dopamine release in the brain that in turn causes repeated or "stereotyped" movements of the head in the animal. (Tr. 885:24-886:5 (Ruffolo).) The tested drug is then administered to the animal, and if the stereotyped movements are potentiated, or increased, this indicates that the drug is increasing dopamine activity in the brain and thereby directly affecting motor behavior. (Tr. 886:6-14 (Ruffolo).)

in Parkinson's patients. (Tr. 886:22-887:3 (Ruffolo).) Moreover, a POSA would have been comfortable relying on this indirect model of Parkinson's disease because no direct models of Parkinson's disease were – or are even today – readily available. (Tr. 887:18-888:6 (Ruffolo).)

The Court further notes that Mylan did not present any expert evidence indicating that undue experimentation would be needed to carry out the method of treatment claimed in the '446 Patent, or that the claims to the use of R(+)-PAI to treat Parkinson's disease reflected only a mere hypothesis. In fact, Mylan presented expert testimony that both the resolution techniques and the animal tests reported in the patent are routine. (Tr. 351:12-352:21; 361:21-362:6 (Castagnoli); see also PTX 1 at 4:36-59 (stating that enantiomer separation could be accomplished by "conventional" means in 1990).) In sum, having considered all of the data disclosed in the patent, including the test results reported for R(+)-PAI and the disclosures regarding the use of (-) deprenyl, the Court holds that the '446 Patent would have enabled a POSA in 1990 to use R(+)-PAI to treat Parkinson's disease. Similarly, based on the information disclosed in the'446 Patent, the utility of R(+)-PAI as a treatment for Parkinson's disease was sufficiently disclosed to enable the claimed invention.

CONCLUSION

For the reasons discussed above, this Court concludes that Mylan has failed to prove, by clear and convincing evidence, that the '446 Patent is invalid for obviousness or for lack of enablement/utility. The parties are directed to submit a Judgment and Form of Order consistent with this Court's opinion.

Dated: September 20, 2013

HON. CLAIRE C. CECCHI
United States District Judge