2021-1070

United States Court of Appeals for the Federal Circuit

NOVARTIS PHARMACEUTICALS CORPORATION,

Plaintiff-Appellee,

– v. –

ACCORD HEALTHCARE INC., AUROBINDO PHARMA LIMITED, AUROBINDO PHARMA USA, INC., DR. REDDYS LABORATORIES, INC., DR. REDDYS LABORATORIES, LTD., EMCURE PHARMACEUTICALS, HERITAGE PHARMACEUTICALS INC., GLENMARK PHARMACEUTICALS INC., USA, GLENMARK PHARMACEUTICALS LIMITED, HETERO USA INC., HETERO LABS LIMITED UNIT-V, HETERO LABS LIMITED, MYLAN PHARMACEUTICALS, INC., PRINSTON PHARMACEUTICAL INC., STRIDES GLOBAL PHARMA PRIVATE

(For Continuation of Caption See Inside Cover)

On Appeal from the United States District Court for the District of Delaware in No. 1:18-cv-01043-KAJ Honorable Kent A. Jordan, Circuit Judge

BRIEF FOR DEFENDANTS-APPELLANTS

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DECEMBER 21, 2020

LIMITED, STRIDES PHARMA, INC., TORRENT PHARMA INC., TORRENT PHARMACEUTICALS LTD., ZYDUS PHARMACEUTICALS (USA) INC., CADILA HEALTHCARE LIMITED, APOTEX INC., APOTEX CORP., SUN PHARMACEUTICAL INDUSTRIES LTD., SUN PHARMACEUTICAL INDUSTRIES INC., SUN PHARMA GLOBAL FZE,

Defendants,

HEC PHARM CO., LTD., HEC PHARM USA INC.,

Defendants-Appellants.

Asserted Claims - U.S. Patent No. 9,187, 405
1. A method for reducing or preventing or alleviating relapses in Relapsing-Remitting multiple sclerosis in a subject in need thereof, comprising orally administering to said subject 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol, in free form or in a pharmaceutically acceptable salt form, at a daily dosage of 0.5 mg, absent an immediately preceding loading dose regimen. 2. The method according to claim 1, wherein 2-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol hydrochloride is administered. 3. A method for treating Relapsing-Remitting multiple sclerosis in a subject in need thereof, comprising orally administering to said subject 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol, in free form or in a pharmaceutically acceptable salt form, at a daily dosage of 0.5 mg, absent an immediately preceding loading dose regimen. 4. The method according to claim 3, wherein 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride is administered. 5. A method for slowing progression of Relapsing-Remitting multiple sclerosis in a subject in need thereof, comprising orally administering to said subject 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol, in free form or in a pharmaceutically acceptable salt form, at a daily dosage of 0.5 mg, absent an immediately preceding loading dose regimen. 6. The method according to claim 5, wherein 2-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol hydrochloride is administered.

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

CERTIFICATE OF INTEREST

Case Number 2021-1070

Short Case Caption Novartis Pharmaceuticals v. Accord Healthcare Inc.

Filing Party/Entity HEC Pharm Co., Ltd., HEC Pharm USA Inc.

Instructions: Complete each section of the form. In answering items 2 and 3, be specific as to which represented entities the answers apply; lack of specificity may result in non-compliance. **Please enter only one item per box; attach additional pages as needed and check the relevant box**. Counsel must immediately file an amended Certificate of Interest if information changes. Fed. Cir. R. 47.4(b).

I certify the following information and any attached sheets are accurate and complete to the best of my knowledge.

Date: 12/21/2020

Signature: /s/ Mieke K. Malmberg

Name: Mieke K. Malmberg

1. Represented Entities. Fed. Cir. R. 47.4(a)(1).	**2. Real Party in Interest.** Fed. Cir. R. 47.4(a)(2).	**3. Parent Corporations and Stockholders.** Fed. Cir. R. 47.4(a)(3).
Provide the full names of all entities represented by undersigned counsel in this case.	Provide the full names of all real parties in interest for the entities. Do not list the real parties if they are the same as the entities. ☑ None/Not Applicable	Provide the full names of all parent corporations for the entities and all publicly held companies that own 10% or more stock in the entities. ☐ None/Not Applicable
HEC Pharm Co., Ltd.		HEC Pharm Group
HEC Pharm USA Inc.		HEC Pharm Co. Ltd.

☐ Additional pages attached

4. Legal Representatives. List all law firms, partners, and associates that (a) appeared for the entities in the originating court or agency or (b) are expected to appear in this court for the entities. Do not include those who have already entered an appearance in this court. Fed. Cir. R. 47.4(a)(4).

☐ None/Not Applicable ☐ Additional pages attached

Steven J. Udick		
Steven W. Hartsell	Skiermont Derby LLP	
Stamatios Stamoulis	Stamoulis & Weinblatt LLC	

5. Related Cases. Provide the case titles and numbers of any case known to be pending in this court or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal. Do not include the originating case number(s) for this case. Fed. Cir. R. 47.4(a)(5). See also Fed. Cir. R. 47.5(b).

☐ None/Not Applicable ☐ Additional pages attached

1:20-cv-00133-LPS	Novartis Pharm. Corp. v. Apotex Inc. et al.	

6. Organizational Victims and Bankruptcy Cases. Provide any information required under Fed. R. App. P. 26.1(b) (organizational victims in criminal cases) and 26.1(c) (bankruptcy case debtors and trustees). Fed. Cir. R. 47.4(a)(6).

☑ None/Not Applicable ☐ Additional pages attached

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TABLE OF AUTHORITIES

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TABLE OF ABBREVIATIONS

Abbreviation	Full Term
(xx:yy-zz)	If this format cites to a patent it refers to column xx, lines yy-zz. If this format is citing to a transcript it refers to page xx, lines yy-zz.
’405 patent	U.S. Patent No. 9,187,405
ANDA	Abbreviated New Drug Application
Appx	Joint Appendix
Argentum IPR	Petition for inter partes review brought against the ‘405 patent in the PTAB by other generics (not HEC). The PTAB’s IPR decisions was appealed before this Court, resulting in an oral argument in front of a Federal Circuit panel. Appx21937-21946. Ultimately this Court issued a limited opinion as to standing due to settlements post-argument between Novartis and certain generics.
cl.xx	Claim no.xx [in cited patent]
Complaint	Complaint for Patent Infringement filed on July 16, 2018 by Novartis
EAE	Experimental Autoimmune Encephalomyelitis or Experimental Allergic Encephalomyelitis
FDA	United Stated Food & Drug Administration

First U.S. Application	Application PCT/EP2007005597 ("First U.S. Application"), filed with USPTO on June 25, 2007, claiming the benefit of priority to the Great Britain application and June 27, 2006 priority date. Appx23768-23805.
Gilenya	Novartis' branded oral fingolimod used to treat RRMS
Great Britain ("GB") Application	Earliest priority date for the '405 patent. Filed on June 27, 2006 Appx23747-23767.
HEC or Appellants	HEC Pharm Co., Ltd. and HEC Pharm USA Inc.
Kappos 2006	Abstract published May/June 2006 announcing Phase II trial administering 0.5, 1.25 and placebo oral fingolimod to RRMS patients. Appx24722-24724 (appearing at Appx24723-24724 – "P569")
Mg	Milligrams
Novartis	Novartis Pharmaceuticals Corporation
Order	Order, Final Judgment, and Injunction (Dkt. 780), entered on September 11, 2020
p.o.	Oral administration
POSA	Person of ordinary skill in the art
PP-MS	Primary Progressive Multiple Sclerosis
PTAB	Patent Trials & Appeals Board

RRMS	Relapsing Remitting Multiple Sclerosis
Second U.S. Application	Application no. 13/149,468 also related to the ‘405 patent and relying on the same shared specification for priority. Ultimately issued as U.S. Patent 8,741,963 (the “‘963 patent”) on June 3, 2014 (never listed in the Orange Book). Appx24258-24299.

STATEMENT OF RELATED CASES

Pursuant to Federal Circuit Rule 47.5, HEC knows of no other appeal in or from this civil action previously before this or any other appellate court. However, HEC believes that the following case may be directly affected by this appeal or directly affect this appeal: *Novartis Pharmaceuticals Corp. v. Apotex Inc. et al.*, C.A. 1:20-cv-00133-LPS.

Furthermore, this Court has considered the sufficiency of the written description in the '405 patent in an appeal relating to an IPR petition in *Argentum Pharma. LLC v. Novartis Pharma Corp.*, 956 F.3d 1374 (Fed. Cir. 2020) (Moore) (*petition for cert. docketed* December 9, 2020) ("Argentum IPR"). In January 2020, this Court heard oral arguments concerning the adequacy of written description, although HEC played no part in that proceeding. Appx21937-21946.

Although the panel expressed deep skepticism concerning the disclosure of one of the claim limitations in the specification, Novartis was able to defeat any adverse decision by settling with certain parties following oral argument. Accordingly, this Court's written opinion in the Argentum IPR was limited to standing issues only. *See id.*; Appx21937-21946.

JURISDICTIONAL STATEMENT

Nearly four years after HEC filed its ANDA No. 207939 seeking to market a generic version of Novartis' branded oral fingolimod (Gilenya) and nearly three years after Novartis listed the '405 patent in the Orange Book, Novartis belatedly sued HEC and 22 other generics in the U.S. District Court for the District of Delaware under 35 U.S.C. §271(e)(2) alleging infringement of the '405 patent. Although Novartis had already brought (and concluded) a suit against HEC on a different fingolimod Orange Book patent, Novartis did not add the '405 patent to that suit, opting instead to bring an entirely new suit on the '405 patent years later. Appx18755 (46:4-49:10); Appx806 (¶238). The district court had jurisdiction as to HEC pursuant to 28 U.S.C. §§ 1331 and 1338(a). After oral argument in the Argentum IPR (brought by other generics, in which HEC played no part) and prior to the scheduled bench trial in this matter, all of the remaining generics except HEC settled with Novartis and withdrew from the litigation.

Following a four-day bench trial, which proceeded only as to HEC, the district court entered its Post-Trial Findings of Fact and Conclusions of Law on August 10, 2020, and entered its Order, Final Judgment, and Injunction disposing of all claims on September 11, 2020. Appx1-42. The district court found Novartis' '405 patent would be infringed, was not invalid, and permanently enjoined HEC from selling or importing the first FDA-approved generic oral

fingolimod. Appx1-5. HEC timely appealed from the final judgment and filed a Notice of Appeal on October 9, 2020. Appx26044-26045. This Court has jurisdiction under 28 U.S.C. § 1295(a)(1).

STATEMENT OF ISSUES

1. The ’405 patent claims recite that 0.5 mg of fingolimod is administered daily “absent an immediately preceding loading dose”. The district court found no recitation or discussion of loading dose in the specification. Did the district court err when it found the ‘405 patent valid under written description when the specification plainly fails to disclose the “absent an immediately preceding loading dose” claim limitation and such exclusion is not necessarily disclosed?
2. The ‘405 patent specification discloses a 12 line hypothetical investigation of clinical benefit, speculating that 20 patients would receive 0.5 mg, 1.25 mg, or 2.5 mg of oral S1P receptor agonist daily and disclosing how to investigate such doses. Yet no results (anticipated, hypothetical or otherwise) were disclosed for any S1P receptor agonist let alone fingolimod, other portions of the specification led away from the 0.5 mg daily dosage, and POSAs agreed that at the time 0.5 mg dosage was considered much too low to be effective. Did the district court err when it found the ‘405 patent valid under written description even when the specification provided no disclosure that any of the doses in the hypothetical investigation of clinical benefit would treat RRMS?

INTRODUCTION

Each of the '405 patent claims includes two limitations: (1) 0.5 mg oral fingolimod to treat RRMS, (2) administered "absent a preceding loading dose." Yet neither limitation is disclosed in the specification. The district court did not find written description support for these limitations in the specification itself. Instead it found alleged support through conflicting expert testimony and attorney argument.

This extrinsic evidence stands in stark contrast to the patent specification, the inventors' testimony, the prosecution history, and the state of the art at the time. Neither Novartis nor the inventors had possession of the 0.5 mg dosage. This is not surprising: as of the '405 patent's 2006 priority date no human had ever been administered a 0.5 mg dose of fingolimod, a dose that was considered too low to be effective. When the FDA requested the 0.5 mg dose added to the Phase III clinical trial which was designed to further test the then lowest known human dose (1.25 mg), clinical investigators balked, believing it was a "bad idea." Appx22712 (134:1-21). Nevertheless, Novartis announced its Phase IIII trial for oral fingolimod through an abstract (Kappos 2006), which provided that 0.5 mg fingolimod, 1.25 mg and placebo fingolimod would be administered to RRMS patients. No results hypothetical or otherwise were disclosed – by all accounts those in the art believed the low dose would not work.

When the results of the clinical trial rolled in and the surprising effects of 0.5 mg on RRMS became known Novartis found itself exposed. The only priority patent application that Novartis had on file at the time was an application relating to inhibiting neo-angiogenesis in other forms of MS (not RRMS) using general S1P receptor modulators (not even fingolimod). Novartis' prosecution odyssey establishes that for years, Novartis filed related applications and gradually moved the ball towards a 0.5 mg treatment for RRMS. It was not until 2014 (four years after Gilenya was approved) that the claims were first included, appearing as out-of-place appendages to the 2006 priority specification.

The specification is silent regarding using or not using loading doses with S1P receptor agonist - that limitation was first added in a related application to get around prior art disclosing the administration of 0.5 mg fingolimod for treatment for MS with a loading dose. The specification is silent as to 0.5 mg dose or its effectiveness in treating RRMS. The priority specification notes a short study relating to laboratory rats induced with EAE (an animal disease mimicking RRMS, depending on the model), and a meager 12 line hypothetical experiment relating to an investigation of clinical benefit (labeled "clinical trial"), which pontificated how to study effects on 20 RRMS patients receiving 0.5 mg, 1.25 mg or 2.5 mg of an S1P receptor agonist by dosing and then conducting a medical examination. The end. There was no disclosure of anticipated or predicted results. No hint or

indication of where the doses came from, or if the inventors possessed (by disclosure) that any dose would treat RRMS. Of course the inventors could not have predicted anything about the so-called "clinical trial." They had no idea where that part of the disclosure had come from, they had no experience or knowledge about clinical trials, and they were solely studying angiogenesis in rats, dosing them with a broad range of doses of fingolimod from 0.1 to 20 mg/kg orally, including a dose of 0.3 mg/kg daily, every 2nd or 3rd day or once a week.

The absence of written description means, quite simply, no valid patent. In the glaring absence of written description evidence, Novartis substituted conflicting expert testimony and argument. Weaving together a rat experiment (with daily dosing and intermittent dosing every other day, every third day, and once a week) and the hypothetical human investigation of clinical benefit with some undisclosed mathematical sleights of hand supplemented with prior art references, Novartis convinced the district court that the inventors selected the claimed weekly dose from the rat experiment (instead of the other disclosed doses), divided by 7 for a daily dose, compared that to the lowest known effective dose in a rat, found it was proportionally 60% less than before, then applied that to the lowest known effective dose in human and *voila*, the claimed 0.5 mg dose was purportedly disclosed in the hypothetical investigation of clinical benefit. But this is not described in the specification.

The problems here are many. The same experts agreed, and the specification reveals, that there is no disclosure in the specification of the mathematics upon which they rely. There is no disclosure for the proportionality upon which they rely. There is no disclosure for any of the lowest known effective fingolimod doses for RRMS upon which they rely – in either rats or humans. There is no disclosure of any motivation to seek the lowest known effective dose. There is no disclosure of the science that translates a weekly dose in rats for a disease that is not RRMS to a daily dose in humans with RRMS. There is, simply, no disclosure of the challenged claim limitations.

Beyond the plain lack of disclosure, the district court's findings about Kappos 2006, the abstract in the same field of art published contemporaneously with the '405 patent, exposes the district court's clear errors. Although the court concluded a POSA would view the patent's recitation of 0.5 mg in a hypothetical investigation of clinical benefit to be effective in humans, the court concluded the exact opposite with regard to Kappos 2006 (which disclosed at least as much, if not more than the patent) and found a POSA *would not understand* that a 0.5 mg dose was likely to work. Appx30-31 (¶¶75-76). Neither the Kappos abstract nor the '405 patent disclose the loading dose limitation. On this the district court agreed, yet it found that silence in the patent meant a loading dose was not used in the claimed method and silence in the abstract (published at the same time in the same

field of art about the same method) somehow meant the exact opposite, e.g. that a loading dose was not necessarily foreclosed.

The district court's revisionist reading of the '405 patent specification to purportedly find: (1) adequate written description sufficient to necessarily foreclose a loading dose where such concept is nowhere discussed – or even mentioned in the specification and (2) adequate written description of the claimed 0.5 mg dose from a rat experiment and featherweight hypothetical investigation of clinical benefit falls far short of the statutorily required written description of the invention in "full, clear, concise, and exact terms". The '405 patent must be invalidated.

STATEMENT OF THE CASE

I. BACKGROUND AND STATE OF THE ART IN 2006

Novartis' '405 patent, titled "*S1P Receptor Modulators for Treating Relapsing-Remitting Multiple Sclerosis*" is presently the last remaining barrier to generic competition to Novartis' branded oral fingolimod, Gilenya, which is used to treat relapsing remitting multiple sclerosis ("RRMS"), a particular form of multiple sclerosis ("MS"). Appx6, Appx24734-24742. Although the '405 patent was not filed until April 21, 2014, it claims priority to June 27, 2006 through a patent application filed in Great Britain ("GB") and a PCT application filed in the United States one year later ("First U.S. Application"). Appx24734. The '405 patent claims are solely directed to a dosing regimen—e.g., orally administering 0.5 mg of fingolimod daily, absent an immediately preceding loading dose, to treat RRMS patients. Appx24741-24742 (cl.1-6). It is undisputed that Novartis in-licensed fingolimod and has no claim to the compound (which has been known since the early 1990s). Appx22607 (7-16).

A. In 2006, the inventors found that a broad class of S1P receptor modulators have inhibitory effects on demyelinating diseases.

MS is an immune-mediated demyelinating disease where the immune system attacks the myelin coating around the nerves in the central nervous system. It is unknown what causes MS, but it is highly debilitating, disrupting the brain, optic nerves, and spinal cord through inflammation and tissue loss. Appx24739-

24740 (8:61-9:12), Appx22696 (7-18). It was well-known that MS presented with four different types of disease patterns, each characterized by the presence or absence of relapses and whether or not the disease seemed to worsen over time. Appx24740 (9:64-10:16). The majority of MS patients initially present as RRMS patients, although eventually many of those patients will develop the secondary-progressive form of MS, experiencing an accumulation of disability. Appx24740 (10:65-11:6).

There exists no permanent cure for MS—the goal is to manage the disease with hope of reducing or preventing relapses and slowing disability. In 2006 there were no oral pharmaceutical treatments for any type of MS. The named inventors found that S1P receptor modulators were a broad class of compounds known to have inhibitory effects on neo-angiogenesis associated with certain demyelinating diseases, like multiple sclerosis and Guillen-Barre syndrome. Appx24740(9:13-15).

B. In 2006, MS was known as an unpredictable disease with unpredictable outcomes in clinical studies, and no human had ever been orally administered a 0.5 mg dose of fingolimod.

Although fingolimod was being studied in 2006 as a potential oral treatment for MS, the disease was (and still is) known as being incredibly unpredictable. Appx30 (¶75), Appx22789-22790 (211:21-212:1), Appx22709 (131:6-9), Appx22697 (119:2-23). Clinical investigators could not predict results of human

clinical trials before running them, and clinical trials were known to fail. Appx15 (¶24), Appx23007 (429:4-25), Appx22755-22756 (177:15-178:14) (failed trials), Appx22830-22831 (252:15-253:3), Appx23397 (819:2-8).

Phase II clinical trials of fingolimod in the treatment of MS had been completed, and the lowest dose used in safety and efficacy trials at that time on humans was 1.25 mg. Appx22692 (114:17-23), Appx22693(115:10-21), Appx22830-22831 (252:21-253:3).

In May/June, 2006, just prior to the '405 patent priority date, Novartis started recruiting for a Phase III pivotal clinical trial of oral fingolimod, with the intention of testing 0.5 mg, 1.25 mg, and placebo on humans. Appx24722-24724. Those skilled in the art did not believe it advisable to administer such a low 0.5 mg dose to humans. Appx22693-22694 (115:22-116:24), Appx22712 (134:1-18), Appx22714 (136:7-10), Appx22715-22728 (137:22-150:7), Appx22735 (157:2-16), 22790 (212:6-13), Appx22735-22738 (157:1-160:8), Appx22789-22790 (211:1-212:14). The 0.5 mg dose had never been administered to humans, and POSAs -including those involved directly in the clinical trials - were skeptical. There was no principled reason to include this 0.5 mg dose for the first time in a large Phase III pivotal trial given the unpredictable nature of the disease, unpredictable outcomes of clinical studies, the immense number of patients and the extensive amount of time required by a Phase III study. *See id*., Appx22693-22694

(115:22-116:24). Testing 0.5mg in the Phase III trial was not a motivation existing in the art but was instead suggested by the FDA in its narrow and agency-specific quest to find the lowest effective doses of drug therapies. Appx22710 (132:2-19). The Phase III study started not long after the GB Application was filed in 2006 but results were not known for four years. Appx2636 (58:16-19). Novartis' 0.5 mg oral fingolimod, Gilenya, was first approved by the FDA for the treatment of RRMS on September 21, 2010.

II. DOSING LIMITATIONS "0.5 MG" AND "ABSENT AN IMMEDIATELY PRECEDING LOADING DOSE" WERE ADDED YEARS AFTER 0.5 MG OF GILENYA WAS FDA-APPROVED

A. The '405 patent and the claims.

The '405 patent is directed to the use of fingolimod in the treatment or prevention of MS. The claims are directed solely to a dosing regimen for fingolimod encompassing a single step—orally administering 0.5 mg of fingolimod daily, absent an immediately preceding loading dose (where a loading dose is a "higher than daily dose") for RRMS treatment. Appx27 (¶63), Appx23344(766:4-6).

Each of the claims differ only in their preambles, e.g. a method for "reducing or preventing or alleviating relapses in RRMS," treating RRMS," or "slowing progression of RRMS." Appx24741-24742 (cl.1,3,5).

Dependent claims add the salt form of fingolimod. Appx24741-24742

(cl.2,4,6).

The precise dosing regimen is the salient feature of the claims yet it is nowhere disclosed in the '405 patent specification. The '405 patent specification does not resemble the '405 patent claims at all. The specification is not directed to particular doses or dosing regimens at all. It is directed establishing that a broad class of S1P receptor modulator, including fingolimod (in the broad class), can inhibit neo-angiogenesis when administered to animals in a broad range of doses.

The '405 patent specification is framed in four distinct parts. The first, and largest portion (9.5 columns), is directed to the chemical makeup of a class of compounds generally known as S1P receptor modulators. Appx24736-24740. This section includes general disclosures about the inhibitory effect of S1P receptor modulators on demyelinating diseases like MS and Guillain-Barre syndrome. Little in the '405 specification is specifically tailored to fingolimod (referred to as Compound A) as a treatment, although the specification discloses generally that fingolimod is useful for treating PP-MS. Appx247401 (10:16-24).

A second, much shorter portion of the specification (a paltry 32 lines), reports the results of a single *in vivo* experiment administering fingolimod in a laboratory rat model of experimental autoimmune encephalomyelitis ("EAE"). Appx24740-24741 (10:32-11:2). EAE is not RRMS, but is known to mimic RRMS and is used in laboratory research. Appx10 (¶5). According to the

specification, EAE was induced in Lewis laboratory rats, resulting in an "acute disease within 11 days, followed by an almost complete remission around day 16 and a relapse at around days 26." Appx24740 (10:35-40). Fingolimod was administered orally ("p.o.") to the rats "at a dose of from 0.1 to 20 mg/kg p.o." Appx24740 (10:60-63). The specification discloses that fingolimod in the hydrochloride salt form "fully blocks disease-associated angiogenesis [in the rats] and completely inhibits the relapse phases when administered daily at a dose of 0.3 mg/kg p.o." Appx24740 (10:65-67). Relapses were also blocked in the laboratory rats when fingolimod was administered "at 0.3 mg/kg every 2nd or 3rd day or once a week." Appx24741 (11:1-2).

The third portion of the specification discloses a hypothetical example of how to investigate clinical benefits of fingolimod in humans. Appx24741 (11:4-16).

Though the bare-bones disclosure is referred to as a "prophetic trial" in the record and is labeled "clinical trial" in the specification, it is hardly more than an outline for a hypothetical investigation of clinical benefit. The prophetic paragraph (a mere 12 lines, not including the title) discloses: (1) 20 patients with RRMS would receive a S1P receptor agonist ("e.g. a compound of formula I, e.g. Compound A") at a daily dosage of 0.5, 1.25 or 2.5 mg p.o. (orally) and (2) patients would be examined weekly and assessed every two months for disease

state and changes in disease progression by radiological and physical examination. Appx24741 (11:20-24). That is the sum total of the prophetic paragraph (and the only mention of a 0.5 mg dose in the specification). Appx23838 (260:2-10), Appx800:10-15.

The prophetic paragraph provides no description or any disclosure whatsoever of a "loading dose" including zero disclosure of any benefits or disadvantages of loading doses. There is no recitation of the form of dosage administered (tablets, capsules, drinks). There is no disclosure of the 20 patients received which dose amount. There is no recitation of any anticipated success or failure for any specific dose amount –only that the "clinical state of the patient is investigated weekly" and that "[d]isease state and changes in disease progression are assessed" so that patients "remain on treatment for as long as their disease does not progress and the drug is satisfactorily tolerated." Appx24741 (11:24-26). Contrary to the very meaning of "prophetic", no hypothesis or predictions were disclosed at all and it would not have been possible to run any type of clinical trial or well-designed experiment within the parameters provided including the lack of placebo. Appx22709 (131:4-19), Appx22840-22841 (262:4-263:7), Appx22709 (131:4-19), Appx23311-23314 (733:22-736:3).

Immediately following this 12 line prophetic paragraph, the specification resorts to a general descriptor of the large – and unknown - variability of daily

dosages of S1P receptor modulators in general. It reports "daily dosages required in practicing the method of the present invention when a S1P receptor modulator alone is used will vary depending on the compound, the host, the mode of administration and the severity of the condition to be treated." Appx24741 (11:20-24). The specification provides an enormous range of possible dosing regimens encompassing the Phase II tested 1.25 mg dose, stating "preferred daily dosage range is about from 0.1 to 100 mg as a single dose or in divided doses" – from less than one tenth the clinically-tested amount to nearly one hundred times the clinically-tested amount. Appx24741 (11:24-26). Although large dosage ranges are provided, the text also indicates "suitable unit dosage forms" for oral administration of S1P receptor modulator "comprise from ca. 0.1 to 30 mg, usually 0.25 to 30 mg S1P receptor modulator, together with diluents carriers." Appx24741 (11:30-35). The specification also states "the S1P receptor modulator, e.g. Compound A [fingolimod]" may be "administered intermittently, e.g., at a dose of 0.5 to 30 mg every other day or once a week". Appx24741 (11:35-38). No data or information is provided concerning whether relapses in RRMS human patients are blocked or alleviated by any S1P receptor modulator (let alone fingolimod) —nor could there be, since the only administration of fingolimod to patients noted in the specification was entirely hypothetical and had never actually been conducted. Appx22 (¶51).

B. The prosecution history.

Every single claim of the ’405 patent is directed to: (1) administering a daily dosage of 0.5 mg of oral fingolimod, (2) absent an immediately preceding loading dose regimen to (3) reduce, prevent, treat, alleviate relapses, or slow the progression of RRMS. But the specification is utterly devoid of even one example of the claimed dosing method and “loading dose” is not mentioned in the specification. There is no description of a loading dose, and there is no description about the presence or absence of a loading dose.

Loading dose is not addressed at all in the specification, and with good reason: the limitations of 0.5 mg daily dose of oral fingolimod and administration absent an immediately preceding loading dose (the entirety of the claimed method) were not added until many years following the 2006 priority date of the ’405 patent specification and well *after* Novartis had received FDA approval for oral Gilenya in the 0.5 mg dosage. The claims were crafted only after the commercial product features were finalized, and shoe-horned into a specification that was never designed to describe the presently claimed invention.

The ’405 patent application was filed April 21, 2014and claims priority to, and shares a specification with, a foreign application filed in Britain on June 27, 2006 listing the same named inventors. Appx24734, Appx23747-23767. Novartis filed its First U.S. Application claiming the benefit of priority to the foreign

application and the June 27, 2006 priority date. Appx23768-23805. The First U.S. Application is generically titled "S1P Receptor Modulators for Treating Multiple Sclerosis." Appx23773. The original 11 claims focused on S1P receptor modulators in general, including compound claims and a kit. Appx23789-23790. Not a single claim recited RRMS, the most common form of MS. Not a single claim was directed to the specifics of dosing, much less dosing an RRMS patient. No claim specified what a "therapeutically effective amount" of any S1P receptor modulator would be to achieve prevention or inhibition of PP-MS (which appeared in the claims) or provided any parameters on how often dosing should occur of any S1P receptor modulator (other than a single method claim calling for administering the S1P receptor modulator "intermittently"). Appx23790 (cl.8-9). Only two claims specified fingolimod, and neither claimed RRMS or any dosing parameters. Appx23790 (cl.10-11). This is unsurprising. Fingolimod's impact on RRMS was largely unknown and nobody had yet dosed RRMS patients with 0.5 mg oral daily dose of fingolimod, which was considered at the time to be too low of a dose to be effective. Appx31 (¶76), *supra* 12.

Novartis' 0.5 mg oral daily dosage of Gilenya in the treatment of RRMS was not approved by the FDA until September 2010—four years after the GB Application was filed. With Gilenya approved, Novartis intensified its efforts to establish a long-term monopoly over the highly lucrative drug. It is plain from the

prosecution history that it was only after the 0.5 mg dosage of Gilenya was approved by the FDA that Novartis began filing a series of related U.S. patent applications all claiming priority back to the 2006 GB Application. Each time Novartis filed a new application, it moved incrementally toward what would become the '405 patent claims by altering the claims and title to eventually include RRMS and the specific FDA-approved dosing parameters of fingolimod, but never changing the original specification on which it relied for priority. Appx23401-23402 (823:22-824:7).

On May 31, 2011, eight months after 0.5 mg daily dosing of Gilenya was approved by the FDA, Novartis filed its Second U.S. Application Appx24258-24299. Novartis titled the Second U.S. Application "S1P Receptor Modulators for Treating Multiple Sclerosis," and submitted new claims. Appx24296-24299, Appx23806-23847, Appx23889-23928; Appx24058-24074, Appx24223-24299. The new claims related to inhibiting neo-angiogenesis of MS by administering 0.5 mg of fingolimod daily. Tellingly, Novartis was five years into prosecution *before setting forth any actual dosing parameters in any claims*.

As with each previous application, no information relating to the specifics of dosing RRMS patients was added to the specification. Appx23602-23603. Although Novartis initially submitted method claims directed to the FDA approved method by claiming "reducing or alleviating relapses in [RRMS] in a subject in

need thereof" by administering a daily dosage of 0.5 mg of fingolimod, those claims were canceled and their applicability to RRMS specifically withdrawn by Novartis. The claims were redrafted to a method "for slowing progression of multiple sclerosis in a subject in the relapsing-remitting phase of *primary progressive multiple sclerosis*" by administering 0.5 mg of fingolimod. *Compare* Appx24926 (cl.15,17) to Appx23889-23891 (cl.15,17).

On February 13, 2013—two years after filing the Second U.S. Application and nearly seven years after the filing of the GB Application, Novartis added, for the first time, "absent an immediately preceding loading dose regimen" to the claims. Appx23889-23891. This language was nowhere to be found in the specification or parent applications, but the reason for the addition was readily apparent—the application stood rejected for obviousness over prior art reference Kovarik disclosing fingolimod administration with a loading dose. Appx23892-23894, Appx23900-23906. Novartis acknowledged its reason for the addition was to avoid prior art:

> Applicants have amended all pending claims (or the claims from which they depend) to specify that the stated daily dosage of 0.5 mg cannot immediately follow a loading dose regimen. Applicants have made these amendments to further distinguish their claims from the disclosure of Kovarik.

Appx23892. This Second U.S. Application issued as U.S. Patent 8,741,963 on June 3, 2014. Appx22672 (94:11-18), 22673 (95:9-23). The '963 patent is

directed towards inhibiting neo-angiogenesis associated with MS and was never listed in the Orange Book.

Just before the '963 patent issued, Novartis filed a continuation application for the '405 patent—its Third U.S. Application—on April 21, 2014. Appx25197-25266, Appx25338-25356, Appx25401-25437. Novartis provided no amendments to the disclosure, but shifted the focus of the Patent Office by changing the title to reference RRMS for the very first time, calling the patent "*S1P Receptor Modulators for Treating Relasping* [sic]*, Remitting Multiple Sclerosis*." Appx25224, Appx24533. Although Novartis included claims for the 0.5 mg daily oral dosing of fingolimod to treat RRMS, the dosage had been awarded FDA approval more than four years after the claimed priority date and similar claims (also filed after the FDA approval) had already been rejected by the patent office and redrafted by Novartis to exclude the applicability to RRMS. Appx25198-252215, Appx25216 (claims). Yet Novartis persisted.

When the Second U.S. Application issued as the '963 patent Novartis amended the claims in the '405 patent application to include the very same "absent an immediately preceding loading dose" language. Appx25401-25404. The very same language which Novartis had previously added in the Second U.S. Application to avoid prior art and to eke out an issuance of the '963 patent. As a result, the very same language that lacked any basis in any preceding priority

application is embedded in the '405 application and persists in the '405 patent claims, which issued on November 11, 2015.

Persistence paid off: the '405 patent will not expire until 2027 unless this Court finds the patent lacks written description.

III. DISTRICT COURT PROCEEDINGS

A. Procedural History

The '405 patent issued in 2015 and was promptly listed in the Orange Book. Although Novartis had just sued various generics for patent infringement related to another Orange Book listed patent (including HEC, who resolved its dispute with Novartis over that patent in 2017), Novartis did not add the '405 patent to the ongoing litigation. Three years later Novartis sued HEC along with 22 other generics for infringing the '405 patent. Appx143-144.

Novartis sat on the '405 patent. Record evidence reveals Novartis believed the '405 patent invalid and was not optimistic about the '405 patent's survival in the Argentum IPR (to which HEC was never a party). Appx17065-17066. Surprisingly - for Novartis and the generics - the PTAB decided the very specific obviousness grounds of the Argentum IPR in favor of Novartis and a few days later, on July 16, 2018, Novartis filed suit against the generics. Appx192.

Definition of a POSA and Claim Construction. During the '405 patent litigation, Chief Judge Stark concluded a POSA is a "multi-disciplinary research

team" including a Ph.D. with expertise in neurology and/or an M.D. with several years of clinical experience treating MS patients as well as a pharmacologist with experience in drug development. Judge Stark construed the claim preambles of a method for "reducing or preventing or alleviating relapses" or "treating" or "slowing the progression of" RRMS, finding that they were "limiting statement[s] of purpose" and construed the "daily dosage of 0.5 mg" of fingolimod as "the amount of drug that someone takes in a given day." Appx11-12, Appx18673-18674.

Preliminary Injunction. Novartis sought a preliminary injunction against HEC and other generics, which was granted in June 2019. Upon Novartis' posting of a bond, all generics were enjoined from launching at risk. Appx19217-19218. While still enjoined, in December 2019, HEC became the first generic to receive final FDA approval for its 0.5 mg generic oral fingolimod.

Trial. Before trial, this case was reassigned to Judge Jordan, a Third Circuit appellate judge sitting by designation. Before opening statements, all of the remaining generics except for HEC executed settlement agreements with Novartis. The four-day bench trial proceeded only between HEC and Novartis. At trial, HEC argued three bases of invalidity of the '405 patent: that there was no written description for either "absent an immediately preceding loading dose" or "0.5 mg daily dosage" of fingolimod under 35 U.S.C. § 112 ¶ 1, and y that the patent claims

were invalid as anticipated under 35 U.S.C. § 102(b) by Kappos 2006. Kappos 2006 is an abstract entitled "Design of a randomized, placebo-controlled study of oral fingolimod (FFTY720) in a relapsing-remitting multiple sclerosis," dated May 27-31, 2006, just before the June priority date of the '405 patent. Appx24722-2472. Kappos 2006 – authored by individuals who are not named inventors on the '405 patent - announced Novartis' plans to conduct a controlled Phase III study of fingolimod, disclosing an intention to administer oral fingolimod daily in 0.5 mg, 1.25 mg and placebo to RRMS patients. Appx24722-24724, Appx27.

In a fashion indistinguishable from the '405 patent specification, the Kappos 2006 abstract makes no mention of a loading dose.

Following trial and post-trial briefing, Judge Jordan found that HEC's ANDA infringed the '405 patent, permanently enjoining HEC from launching its FDA approved generic fingolimod. Appx1-4, Appx42. Judge Jordan also found that the '405 patent's written description supported both claim limitations requiring "absent an immediately preceding loading dose" and "0.5 mg daily dosage" of fingolimod. Appx32-33. Judge Jordan further found that Kappos 2006 was not prior art because there was no evidence it was publicly available in June 2006 and, regardless, the reference was not anticipatory based on a lack of enablement. Appx33-35.

HEC appeals the district court's judgement with respect to written

description. While HEC is not appealing the district court's decision finding that Kappos 2006 is not prior art, Kappos 2006 and the district court's corresponding findings maintain relevance in this appeal. Judge Jordan made factual findings regarding the understanding of a POSA reading Kappos 2006 as of the '405 patent priority date, and many of those findings are inapposite and impossible to comport with the district court's findings regarding the understanding of a POSA reading the '405 patent at the exact same time. The district court's findings with respect to Kappos 2006 exposes clear errors made by the district court in assessing written description, and for this reason Kappos 2006 and corresponding district court findings are relevant here.

B. The District Court's Final Judgment

1. The district court found "no mention of loading dose" in the specification, yet determined that silence equated to disclosure.

Although the district court correctly and indisputably found "no recitation of a loading dose in the specification," (Appx26 (¶61)) and further found that the '405 patent "does not describe loading doses," (Appx27 (¶¶64-65)) the district court inexplicably determined that the negative claim limitation "absent an immediately preceding loading dose" was, somehow, supported by the specification. Appx37-38 (¶24). The patent specification is silent on loading doses, yet the district court determined the silence alone informed a POSA that a loading dose was excluded from the invention. Appx26 (¶61).

The district court premised its finding, not on what was contained within the specification, but instead on what was absent from the specification. Appx27 (¶66). The conclusion that a POSA reading the patent would not expect a loading dose to be used when treating RMMS with fingolimod is legally erroneous and plainly wrong. Novartis' own expert witness, Dr. Lublin, contradicted this very finding, testifying that the 0.5 mg daily dosage does not necessarily exclude a loading dose from the perspective of a POSA (Appx22872-22873 (294:25-295:4)) and Novartis' Dr. Jusko also testified one could "envision the possibility of starting with a loading dose." Appx23475-23476 (897:18-898:10). Loading doses were routine in the art - indeed, if it weren't for prior art teaching the utility of having loading doses with fingolimod, Novartis would not have written the negative claim limitation into the claims in the first place. Appx23897.

Just like the '405 patent specification, the Kappos 2006 abstract also makes no mention of loading doses. Appx28 (¶74). Although the district court found that silence in the specification concerning a loading dose apparently informed a POSA that the loading dose was excluded from the invention, the district court did not extend the same understanding to the Kappos 2006 abstract. Instead, in diametric opposition to the district court's findings with respect to the silence in the specification, the district court found that the failure to mention the loading dose in Kappos 2006 "*does not* preclude the use of a loading dose in the clinical trial it

described." Appx41 (¶37), Appx25 (¶74)

2. **The district court found written support for the 0.5 mg dose based on incorrect assumptions, not the specification itself.**

The district court also found that the '405 patent specification supported the 0.5 mg daily dosing of fingolimod for treating human RRMS patients. First, the court found that the prophetic paragraph in the specification provided written support for the 0.5 mg dosing of fingolimod for the purpose of treating RRMS. Appx21-22 (¶49). The court based its determination on a finding that a POSA would understand the prophetic paragraph "assumes that the daily dosage of 0.5 mg is an effective treatment." Appx21 (¶49). Yet no human had ever received a 0.5 mg daily dose of fingolimod as of the priority date of the '405 patent, the hypothetical trial was never conducted, and there were no results demonstrating the effectiveness of a 0.5 mg daily dose of fingolimod in humans.

Other findings by the court contradicted the assumption that a POSA in June 2006 would have believed a 0.5 mg daily dose of fingolimod would be an effective treatment, prior to any actual testing. The district court made express findings that MS is an unpredictable disease, that studying it is difficult, that clinical trials often fail, and that there is simply no way to know in the beginning of a trial what the answer will be (e.g., whether a dose will be effective or not). Appx30 (¶75), Appx15 (¶24). These findings hold true for the 0.5 mg dosage of fingolimod: Novartis' own clinical investigator, testifying as a POSA, told the court that he had

no idea if 0.5 mg would be effective or not until the trial was completed. Appx15 (¶¶23-24), Appx30-31 (¶¶75-76), Appx22962-22694 (114:14:116:24).

In evaluating the specification for disclosure concerning the 0.5 mg dosing of fingolimod, the court considered just two parts of the already meager specification—the EAE portion directed to laboratory rats and the 12 line prophetic paragraph. The EAE portion of the specification does not mention 0.5 mg daily dosing or any human subject in need thereof, but instead sets forth a dose in laboratory rats of 0.3 mg/kg weekly. This dosage of fingolimod was found to inhibit the relapse phase of artificially induced EAE in rats, not actual RRMS in humans. Appx24740-24741 (10:67-11:2), Appx23374 (796:3-797:8). Nevertheless, the district court found, based solely on expert testimony and not on the content of the patent, that a POSA would have understood that the 0.5 mg dose alone somehow came from the EAE experiment. Appx23-26. There is no mention in the district court's order of the other doses that were also given to the rats and which also had similar effects, including 0.3 mg/kg daily, as well as 0.3 mg/kg administered every 2nd or 3rd day. Appx24740-24741 (10:64-11:2).

In order to draw such correlation, the court made findings grounded solely in Novartis' expert testimony and unsupported by the patent specification itself. The court found that a POSA would recognize that the 0.3 mg/kg weekly in rats is "approximately 60% lower" than the lowest known effective dose known in the

prior art (0.1 mg/kg daily). Appx25 (¶57). Then, using this newly-identified proportionality, the court found that 60% of the lowest effective dose known in humans (1.25 mg) would somehow translate to the 0.5 mg dose mentioned in the prophetic trial. Appx25 (¶58). The court concluded – without any supporting evidence in the plain text of the specification or even from the inventors themselves - that a POSA would understand that the inventors translated the lowest known effective dose administered weekly in rats (appearing in the EAE portion of the specification) to the 0.5 mg daily dose in humans (appearing in the prophetic clinical trial portion of the specification). Appx25 (¶59).

The court ignored other express disclosures concerning the unpredictability of the subject matter and a large variability in dosages of S1P receptor modulators. The specification itself notes daily dosages will vary greatly based on compound, administration and severity of the condition to be treated. Appx24741 (11:20-24). The "preferred daily dosages [of S1P receptor modulators] range from 0.1 to 100 mg" (Appx24741 (11:24-25)) and "suitable unit dosage forms for oral administration comprise from ca. 0.1 to 30 mg, usually 0.25 to 30 mg S1P receptor modulator." Appx24741 (11:31-34). Additionally, the specification reported "Compound A [fingolimod] may alternatively be administered intermittently, e.g. at a dose of 0.5 to 30 mg every other day or once a week." Appx24761 (11:35-38). Instead, the court plucked the singular 0.5 mg reference out of the prophetic

paragraph – which also disclosed 1.25 mg and 2.5 mg doses of S1P modulators in general - and concluded that the inventors chose the lowest effective dose in the EAE rat experiment (which was once weekly), translating it to a 0.5 mg dose in the hypothetical trial. Appx24741 (11:35-38), Appx25 (¶59). There is nothing patent tethering the EAE rat experiment to the 12 line prophetic paragraph nor could the inventors provide any insight – neither had any knowledge of the prophetic paragraph nor any experience in clinical trials. Appx22890-22912 (312:6-334:8), Appx22915-22920 (337:15-342:11), Appx22928-22930 (350:11-352:18). Yet the district court found the EAE experiment and the prophetic trial "'complementary' when read in the context of the entire patent," tying them together based solely on Novartis' expert testimony that in "the animal experiment they said we've got it; a lower dose of fingolimod will work. They … make the conversion to human dosing, and then *they show this clinical trial and that they're treating it. That's how I read the patent*." Appx23 (¶53). But nothing was being treated in the hypothetical trial and there was no evidence that the 0.5 mg dose (or any dose for that matter) would work in RRMS patients, whether with or without any loading dose. The specification does disclose any inventor realization that they had discovered the effectiveness of "low-dose" fingolimod – neither those words or even the concepts are ever disclosed in the specification. The lack of disclosure relating to the 0.5 mg dose is expected and unsurprising - in June 2006 nobody had

ever been administered the 0.5 mg dose and the experiment mentioned in the prophetic paragraph was never conducted. Appx22841 (263:8-23), Appx22850 (272:3-11).

While the patent specification is conspicuously silent on any relationship, the named inventors themselves were similarly unhelpful in revealing any actual relationship. The named inventors testified that they had absolutely no idea where the prophetic trial portion of the specification came from, that neither inventor had any experience in designing or running clinical trials, and that there is no disclosure in the '405 patent concerning any conversion of the EAE animal study to human dosing. Appx22890-22912 (312:6-334:8), Appx22915-22920 (337:15-342:11), Appx22928-22930 (350:11-352:18). The district court ignored this inventor testimony, instead concluding that the inventors were in possession of the invention despite a plain lack of description for it in the specification which was acknowledged by the court. Appx37 (¶24).

Although the court found that a POSA would "assume" that the 0.5 mg dose in the hypothetical investigation was an effective dose, the court found the opposite with respect to Kappos 2006. Kappos 2006 disclosed the Phase III clinical trial design where a 0.5 mg daily dose of fingolimod would be administered to patients with RRMS, yet the court found that the abstract announcing the trial (which was actually later run according to plan) was "too theoretical" (Appx41-42, ¶38) and

that a POSA would not understand that a 0.5 mg dose was likely to work. Appx30-31, ¶¶75-76.

IV. POST-TRIAL MOTIONS

After this appeal was docketed and just before this brief was filed, the district court issued two additional orders in favor of Novartis. The district court declined to stay the reset of HEC's ANDA pending this appeal and agreed to extinguish HEC's claim to the bond. Appx26195-26213. HEC remains the only generic with final approval and the only generic that can possibly enter the market once the '405 patent is invalidated.

V. FOR THE SECOND TIME THE FEDERAL CIRCUIT WILL FRUITLESSLY COMB THE SPECIFICATION LOOKING FOR EVIDENCE OF THE PHANTOM LOADING DOSE LIMITATION

This is not the first time a Federal Circuit panel has considered the '405 patent and the lack of "absent an immediately preceding loading dose" in the specification. In January 2020, just before the bench trial in this case, a Federal Circuit panel heard oral argument in the Argentum IPR. Appx21937-21946. During oral argument, members of the panel expressed strong skepticism that any support for the negative claim limitation appears in the specification, stating unequivocally during argument that "this is a claim limitation and it isn't found in the 206 – 2006 application." Appx21941 (13:1-3), Appx21941 (13:19-20) ("But wouldn't you say that even a negative limitation *has to find support in the*

specification." (emphasis added)). Although Novartis argued to this Court that it was inherent to the specification based on the understanding of a POSA, a panel member retorted: "doesn't that leave a person of skill in the art guessing and – and just searching for a needle in the haystack?" Appx21942 (17:9-11). Novartis, presumably saw the writing on the wall and settled with the remaining generic-appellants who still held standing shortly after the oral argument. The written description issue mooted, the Federal Circuit's opinion addressed the threshold standing issue.

SUMMARY OF ARGUMENT

A patent specification must set forth the invention claimed in "full, clear, concise, and exact terms." §112 ¶1. Failure to do so renders the claims invalid. Here, every claim of the '405 patent requires the administration of 0.5 mg daily dosage of oral fingolimod "absent an immediately preceding loading dose" to treat RRMS patients.

Although the district court was admittedly unable to find any disclosure relating to loading doses, the court refused to render the claims invalid under written description. Instead, the district court found that silence in the specification as to loading doses would inform a POSA that loading doses were excluded. This was clear error, particularly where Federal Circuit precedent holds that silence cannot serve as a basis for exclusion. Furthermore, both prior art

(which precipitated Novartis' addition of the loading dose limitation to gain allowance) and Novartis' own expert testimony at trial established that loading doses were in fact used with fingolimod and that mere silence does not necessarily exclude them. The district court's error was compounded by its findings with respect to Kappos 2006 – an abstract published contemporaneously with the patent and which announced Phase III trials for 0.5, 1.25 and placebo oral fingolimod. Kappos 2006 does not mention loading doses either, yet the district court found that silence would inform a POSA that a loading dose could not be foreclosed. This logical inconsistency also amounts to clear error.

The district court also clearly erred when it found the specification disclosed a 0.5 mg daily dose of oral fingolimod as a treatment for RRMS. Although the patent states that 0.3 mg/kg daily, every other day, every third day and weekly doses of fingolimod were effective in laboratory rats subjected to EAE, there is nothing in the specification that shows that 0.5 mg of fingolimod would be used to treat patients suffering from RRMS. In fact, POSAs at the time viewed the 0.5 mg dose as too low to be effective.

The district court wove together a hypothetical investigation of clinical benefit that provided no expected results with the EAE rat experiment to find disclosure that is not in the four corners of the specification. Relying solely on conflicting expert testimony (unsupported by the inventors) and undisclosed

mathematical contortions and translations (which the experts testified did not add up), the district court found that 0.5 mg daily dose in humans to treat RRMS was adequately disclosed in the specification. This was error, particularly where there is nothing in the specification showing the inventors' possession. No disclosure connected the two parts or stated they had discovered "low-dose" fingolimod as an RRMS treatment.

ARGUMENT

I. STANDARD OF REVIEW

Compliance with the written description requirement of 35 U.S.C. § 112 ¶1 is a question of fact, reviewed for clear error following a bench trial. *See Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1566 (Fed. Cir. 1997). The written-description analysis turns on underlying legal principles, which are reviewed *de novo*. *See e.g., Braintree Labs., Inc. v. Novel Labs., Inc.*, 749 F.3d 1349, 1358 (Fed. Cir. 2014); *Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1376-79 (Fed. Cir. 2017) (finding legal error in jury instructions regarding written description test); *Alcon Research Ltd. v. Barr Labs., Inc.*, 745 F.3d 1180, 1186 (Fed. Cir. 2014) ("a factual finding is clearly erroneous when, despite some supporting evidence, we are left with a definite and firm conviction that the district court was in error.").

II. WRITTEN DESCRIPTION IS A TEXTUAL INQUIRY, FOCUSED ON THE FOUR CORNERS OF THE SPECIFICATION

The Patent Act requires, as a condition of a patent, that "[t]he specification shall contain a written description of the invention" and in "full, clear, concise, and exact terms". 35 U.S.C. § 112, ¶1. Whether or not the specification discloses the claimed invention is a textual, "'objective inquiry into the four corners of the specification from the perspective of one of ordinary skill in the art." 35 U.S.C. § 112, ¶1; *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010); *Carnegie Mellon Univ. v. Hoffman-La Roche Inc.*, 541 F.3d 1115, 1122 (Fed. Cir. 2008) ("written description is met by disclosure in the specification of the patent."). The requirement is satisfied only if the inventor "convey[s] with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention …" *Centocor Ortho Biotech, Inc. v. Abbott Labs.*, 636 F.3d 1341, 1348 (Fed. Cir. 2011) (citation omitted); *Ariad*, 598 F.3d at 1351 (the patent specification must objectively demonstrate possession of the invention, describing the invention so that it is understandable to a skilled artisan, and "show[s] that the inventor actually invented the invention claimed."). Even "actual 'possession' or reduction to practice outside of the specification is not enough. Rather, . . . *it is the specification itself that must demonstrate possession.*" *Id.* at 1352 (emphasis added). The written description inquiry is focused on the specification and cannot be fulfilled by the claim language; the claims themselves

(no matter when they are added) must be individually supported and disclosed in the specification to which they claim priority. *Id.* at 1351; *Bradford Co. v. Conteyor N. Am., Inc.*, 603 F.3d 1262, 1269 (Fed. Cir. 2010).

Accordingly, in exchange for fully, clearly, concisely, and exactly disclosing the invention, the inventor is granted a monopoly. In this way, patent protection is awarded to those who actually perform the difficult work of "invention": conceive of the complete and final invention with all its claimed limitations *and* disclose the fruits of that effort to the public. *Ariad*, 598 F.3d at 1353; *see also In re Wallach*, 378 F.3d 1330, 1335 (Fed. Cir. 2004) (invention must be disclosed in a way that clearly allows a POSA to recognize the inventor invented what is claimed and possessed the claimed subject matter at the date of filing); *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 920 (Fed. Cir. 2004) (holding that the purpose of the written description requirement is to "ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification") (quoting *Reiffin v. Microsoft Corp.*, 214 F.3d 1342, 1345 (Fed. Cir. 2000)); *ICU Med., Inc. v. Alaris Med. Sys., Inc.*, 558 F.3d 1368, 1376-77 (Fed. Cir. 2009) (same). Although expert testimony may help shed light on the understanding of one skilled in the art reading the disclosure, testimony cannot wholesale supplant the specification. This would defeat the very basis of the bargain. *See U.S. v. U.S.*

Gypsum Co., 333 U.S. 364, 396 (1948) (for clear error review, testimony in conflict with contemporaneous documents is given little weight, particularly where crucial issues involve mixed questions of law and fact); *Nuvo Pharm. (Ireland) Designated Activity Co. v. Dr. Reddy's Labs. Inc.*, 923 F.3d 1368, 1381 n.4 (Fed. Cir. 2019) (*cert. denied*, 140 S. Ct. 902 (2020)) ("Dispositively, [expert] testimony is irrelevant to the written description inquiry, because it does not point to any disclosure in the specification to which the testimony could relate."). Accordingly, insufficient disclosure is alone a basis to invalidate issued claims. *Univ. of Rochester*, 358 F.3d at 927.

III. THE DISTRICT COURT CLEARLY ERRED WHEN IT FOUND THERE WAS DISCLOSURE OF "ABSENT AN IMMEDIATELY PRECEDING LOADING DOSE", DESPITE HAVING DETERMINED THERE WAS NO RECITATION OR SUPPORT FOR THAT LIMITATION IN THE SPECIFICATION

Each of the claims of the '405 patent is directed to a method of treating, alleviating, reducing, or preventing RRMS relapses by administering 0.5 mg of oral fingolimod to a patient "absent an immediately preceding loading dose." It is undisputed that there is "no recitation of a loading dose in the specification," (Appx26 (¶ 61)) and the '405 patent "does not describe loading doses," (Appx27 (¶ ¶64-65)). A Federal Circuit panel independently scoured the '405 patent specification earlier this year looking for support for the negative claim limitation and, like the district court, came up empty handed.

Simply put, there is no disclosure whatsoever for "absent an immediately preceding loading dose"—or any disclosure of a loading dose or its potential benefits or disadvantages at all. This alone should be enough to end the inquiry and confirm a failure to comply with 35 U.S.C. § 112, ¶1 as a matter of law.

The district court ignored this court's precedential legal authority (it cited no written description authority whatsoever for the negative claim limitation beyond *Ariad*), and its own incongruous findings when it determined the "absent an immediately preceding loading dose" limitation was adequately disclosed. This was clear error as a matter of law.

A. The district court ignored Federal Circuit precedent.

The district court based its determination—not on the content of the specification (which is completely silent as to the negative claim limitation)—but instead on conflicting expert testimony delivered in a courtroom 14 years post-priority. Citing to a few lines of expert testimony – which contradicted Novartis' other experts and prior art - the district court made an erroneous factual finding that a POSA reading the patent would not expect a loading dose to be used when treating RRMS with fingolimod. Appx27 (¶66). Thus the district court held, a POSA would understand from reading the specification that the negative claim limitation was adequately disclosed. This was reversible error because the district court did not find that the negative limitation was necessarily disclosed in the

specification.

This Court maintains clear precedent which *requires* written description support for a negative claim limitation. Where a negative claim limitation is at issue, the specification must "describe[] a reason to exclude the relevant limitation." *Inphi Corp. v. Netlist, Inc.*, 805 F.3d 1350, 1355 (Fed. Cir. 2015) (emphasis added) (quoting *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1351 (Fed. Cir. 2012) (*en banc denied*)). While Novartis is entitled to narrow claims (if the narrowed claims are supported by the specification), Novartis may not plunk negative claim limitations into a claimed invention without tethering it to the written description. Yet this is exactly what Novartis did. When prior art presented a basis for examiner rejection Novartis found a way around – but that was in error which this court can remedy.

It is well-settled law that silence alone cannot serve as a basis for exclusion. This Court holds that a POSA must be able to recognize from the priority application itself that the claimed exclusion was *specifically intended as of the priority date*. *See Santarus*, 694 F.3d at 1351 (holding the patent valid under written description because "[n]egative claim limitations are adequately supported when the specification describes a reason to exclude the relevant limitation."). The "specific intention" behind the exclusion may be recognized in a myriad of ways. In *Santarus*, the specification "expressly list[ed] the disadvantages of using" the

excluded limitation, which was sufficient for disclosure. 694 F.3d at 1351. In *Inphi Corp.*, on the other hand, the specification described alternative features, which this Court held was also sufficient for disclosure. 805 F.3d at 1357. Although there may be several ways to meet the written description for a negative claim limitation *silence is not sufficient disclosure*. *See* MPEP §2173.05(i) ("Any negative limitation or exclusionary proviso must have basis in the original disclosure . . . [t]he mere absence of a positive recitation is not a bases for an exclusion.").

The district court completely ignored this Court's precedential authority requiring affirmative express disclosure, choosing, instead, the deafening silence that comes with no disclosure whatsoever. The district court relied on a single expert's statement plucked from the thousand-page trial record and delivered more than 14 years post-priority *about Kappos 2006- not the '405 patent specification-* to justify, retroactively, the exclusion of the loading dose from the specification. Appx27 (¶66) (incorporating Appx23129 (551:6-12), Appx23126-23127 (548:2-549:2)). Such post-priority reliance based on testimony directed to the prior art, not the specification, is particularly tenuous where, as here, there was conflicting testimony, much of it delivered from Novartis' own experts, and no supporting testimony from the inventors. Novartis' experts testified that a loading dose would not necessarily be excluded when treating with fingolimod and another testified he

could "envision the possibility of starting with a loading dose." Appx22872-22873 (294:25-295:4) (Lublin agreeing nothing in text discloses rationale for prohibiting loading dose), Appx23475 (897:14-898:10) (Jusko: "I could envision starting with a loading dose"), Appx23510 (932:8-14) (Q: "you could see giving a loading dose when one moved down to a lower dose . . ." A:"Yes."). They also agreed there was no disclosure of loading dose or a corresponding rationale to include or exclude loading doses. Appx22846-22847 (268:22-269:1), Appx22834 (256:11-14), Appx23404-23406 (826:6-828:4)

The trial record reflects that the exclusion of a loading dose when administering fingolimod was far from universally accepted and thus mere silence in the specification could not *necessarily* disclose the negative claim limitation. This is consistent with prior art cited during prosecution disclosed the administration of fingolimod *with a* loading dose and which precipitated Novartis' seven-year post-priority date addition of the claim language "absent an immediately preceding loading dose" for the first time during prosecution. *Supra* 21, Appx23889-23891. Thus the court's finding that a POSA would not expect a loading dose when treating RRMS with fingolimod, and then imputing that finding into the entire patent with no textual support whatsoever is contrary to the weight of the evidence, at odds with the specification itself, clearly erroneous as insufficient to meet the legal requirements of written description. *See Inphi Corp.*,

805 F.3d at 1356 (patentees may not "arbitrarily dissect its invention by amending the claims in order to avoid the prior art."); *see also In re Jones*, 10 Fed. App'x 822, 828 (Fed. Cir. 2001) ("the missing descriptive matter must be *necessarily* present . . . Inherency 'may not be established by probabilities or possibilities.'") (*quoting Continental Can Co. USA Inc. v. Monsanto Co.*, 948 F.2d 1264, 1268-1269 (Fed. Cir. 1991); *see also PowerOasis, Inc. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1306-07 (Fed. Cir. 2008) (collecting cases).

B. The district court's order is logically inconsistent, warranting reversal.

Despite prior art and Novartis' expert testimony confirming that loading doses were used with fingolimod, the district court determined that silence in the specification would purportedly inform a POSA that loading doses w*ere excluded from the claimed invention*. Appx27 (¶66). Yet it is the district court's own counter-findings with respect to the Kappos 2006 abstract which lays bare the fatal and facial inconsistency in the court's logic. Kappos 2006, which announced Novartis' Phase III clinical trial wherein RRMS patients would be administered 0.5 mg, 1.25 mg oral fingolimod and placebo, was published contemporaneously with the filing of the priority application. The district court found that Kappos 2006, *like the '405 patent specification, was also silent as to loading doses*. Appx30 (¶74). Yet the district court was inconsistent in determining what a POSA in 2006 would understand when reading the '405 patent specification versus Kappos 2006.

Although the district court determined that silence in the '405 patent specification informed a POSA that *the loading dose was excluded* from the invention, the district court determined that the same silence in Kappos 2006 would *inform a POSA exactly the opposite that a loading dose may have been* used. Appx30 (¶74), Appx27 (¶66). Both conclusions cannot simultaneously hold true.

The district court's internal inconsistency, combined with the absence of any disclosure supporting "absent an immediately preceding loading dose" in the '405 patent, forces inevitable invalidity of the '405 patent. *See Anderson v. City of Bessemer City*, 470 U.S. 564, 574 (1985) ("Where there are two permissible views of the evidence, the factfinder's choice between them cannot be clearly erroneous."); *see also*, *Honeywell Int'l Inc. v. Mexichem Amanco Holding S.A.*, 865 F.3d 1348, 1354 (Fed. Cir. 2017) (vacating and remanding a PTAB decision because its analysis of inherency and unpredictability were internally inconsistent); *Ferring B.V. v. Watson Labs., Inc.-Fla.*, 764 F.3d 1401, 1410 (Fed. Cir. 2014) (reversing infringement finding inconsistent with district court's statement that an ANDA amendment narrowing a hardness range would avoid infringement); *Linear Tech. Corp. v. ITC*, 566 F.3d 1049, 1064-65 (Fed. Cir. 2009) (vacating non-infringement finding because ITC's reliance on a particular limitation was internally inconsistent); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986) (reversing internally inconsistent judgment of

invalidity).

In an attempt to justify its internal inconsistency, the district court imparted a legally unsupported and novel assumption that a patent is presumed "complete" and thus contains all of the "necessary" information, yet an abstract is incomplete and does not include all of the "necessary" information. Appx30 (¶74). In this way the district court implied that a POSA would read patents and abstracts in the same field of art and in the same time frame differently and inconsistently. Yet there is no basis to support entirely different readings of references, abstracts or patents in the same field of art by a POSA in June 2006-and even if there was, the disclosure that counts for written description must be in the specification.

The district court appeared to derive its presumption of completeness—not from precedential legal authority (none exists)—but from short portions of expert testimony presented by Novartis. Novartis' pharmacology expert, Dr. Jusko, gave incoherent testimony that an abstract is "inherently incomplete", but that a "publication and a patent are presumed complete", and a third category of "more extensive reports that are extremely thorough" including clinical trial protocols and unnamed reports, are "sent to the FDA." Appx23474-23475 (896:7-897:13), Appx22782-22783 (204:16-205:1). Based on this testimony the district court rendered the two countervailing and inapposite findings: (1) that a POSA reading the '405 patent specification would understand that it was complete and thus the

absence of a loading dose was necessarily disclosed (e.g., absence of evidence is evidence of absence); and (2) a POSA reading the Kappos 2006 abstract would understand the abstract was not complete and thus the absence of a loading dose indicates that it may have been used. Appx30 (¶25), Appx26 (¶61). But none of these experts were qualified as experts in patent law and their testimony imputes no presumption of "completeness" as to any disclosure.

Here, the district court's incorrect presumption that the '405 patent is "complete" prevented it from seriously testing validity under this Court's written description precedent. This led the court to logically inconsistent conclusions, particularly with respect to the disclosures in the '405 patent specification versus the disclosures in the Kappos 2006 abstract. This error was fatal to the district court's final judgment as to validity, requiring a complete reversal as a matter of law.

IV. THE DISTRICT COURT ERRED IN FINDING THE CLAIMED 0.5 MG DOSE OF FINGOLIMOD IN THE WRITTEN DESCRIPTION

The '405 patent claims administering 0.5 mg of fingolimod for the purpose of addressing RRMS. The preambles of the claims were construed as "limiting statements of purpose" and the trial judge understood that the claims required effectiveness of the 0.5 mg dosage of fingolimod in treating RRMS. Appx11-12 (¶10), Appx21 (¶49), Appx25 (¶58). The district court looked to two places to cobble together support for the claimed dosage: (1) the EAE experiment conducted

on laboratory rats, which tested only 0.3 mg of fingolimod/kg administered *weekly to laboratory rats induced with EAE* - not humans with RRMS and (2) the 12-line hypothetical experiment (misleadingly labeled "clinical trial"), which was never conducted and which speculated that 20 RRMS patients would receive a S1P receptor agonist at daily dosages of 0.5 mg, 1.25 mg or 2.5 mg and then medically examined. Besides speculating that patients might be examined, no other information is provided concerning any anticipated results or whether or not any of the multiple dosages disclosed would treat RRMS. Appx24741 (11:6-16).

Neither portion of the specification discloses the entirety of the claim limitation and nothing tethers 0.3 mg/kg of fingolimod administered weekly in rats to a 0.5 mg dose administered daily in humans – certainly nothing that approaches "full, clear, concise, and exact terms" required of written description. 35 U.S.C. § 112, ¶1. Yet the district court incorrectly fused laboratory animal data with an untested and unproven hypothetical example, rather than properly considering the actual four corners of the specification. This was clear error.

A. The district court's findings and the record confirm that a POSA in 2006 would not have expected to treat RRMS with a 0.5 mg dose of fingolimod, and no patient had ever been so treated.

The patent discloses that 0.3 mg/kg weekly dosage was shown effective in rats with EAE, but nothing in the specification demonstrates that 0.5 mg of oral fingolimod would be effective in humans suffering from RRMS. This is

unsurprising because as of the priority date of the ’405 patent, no human had ever been dosed with 0.5 mg of oral fingolimod. Appx22766 (188:9-18). Appx22768-22770 (190:14-192:7). Moreover, as the district court found and the record reflects, MS was a difficult and unpredictable disease to study, there was simply no way to gauge pharmaceutical effectiveness on MS (or RRMS) until the results of a clinical trial were in (and trials were well-known to fail) and, at the time, those skilled in the art believed that 0.5 mg of fingolimod was too low of a dose to be effective. *Supra* 12. In fact, as the court found, a POSA knew that if the dose was not high enough then fingolimod would provide no benefit. Appx31 (¶76), Appx23469-23470 (891:10-892:6). At the time, the lowest known effective dose in the art was 1.25 mg (although this was not disclosed in the ‘405 patent specification). Appx22693 (115:16-21). And it was only at this time in the art (May/June 2006)– without prior data and facing unpredictability - that Novartis announced, through Kappos 2006, its intentions to proceed with a Phase III trial where it would test for the first time 0.5 mg of oral fingolimod. At this point Gilenya was still four years away from FDA approval in the 0.5 mg dose and many in the art viewed attempts to test the 0.5 mg dose as problematic. *Supra* 12.

Nevertheless, the district court found disclosure where there is none, directly contradicting key factual findings concerning the state of the art at the time of the invention. The district court, crediting expert testimony, found that the “prophetic

trial in the patent assumes that the daily dosage of 0.5 mg is an effective treatment . . ." (Appx21 (¶49)) and that the prophetic trial "provides anticipated results from treatment." Appx22 (¶51). But "assuming" effectiveness is insufficient for confirming compliance with written description. Written description is not satisfied by "assumptions" absent disclosure, particularly where the evidence and fact findings indicate a POSA would not have expected the 0.5 dosage to be effective in light of the difficulty and unpredictability of MS treatments and clinical trials. Appx25 (¶75), Appx15 (¶24) *supra* 12, *Nuvo Pharm.*, 923 F.3d at 1381 (written description insufficient where a POSA would not have expected uncoated PPIs to be effective and specification did not teach otherwise); *Zoltek Corp. v. U.S.*, 815 F.3d 1302, 1308 (Fed. Cir. 2016) (written description applied in the context of the state of the knowledge at the time of the invention).

Contrary to the district court's findings that the hypothetical trial "provides anticipated results from treatment" (Appx22 (¶51)), the specification plainly demonstrates that the prophetic paragraph provides no results, anticipated or otherwise, to inform what the clinical benefit – if any - might be to any patient receiving the 0.5 mg dose of fingolimod. Appx22865-22866 (287:3-288:6). The text of the disclosure speculates only that 20 patients may receive oral S1P modulator in 0.5, 1.25 or 2.5 mg daily doses for two to six months and postulates the patients would be medically evaluated for disease state and changes.

Appx24741 (11:8-12). Although the prophetic paragraph provides that patients would "remain on treatment for as long as their disease does not progress and the drug is satisfactorily tolerated" no disclosure provides which of the three doses, if any, would treat disease progression. Appx24741 (11:13-16), Appx22811-22812 (233:23-234:8), Appx22819 (241:12-24), Appx22822 (244:11-16), Appx22823 (243:21-25). This is insufficient to support written description. *See Biogen Int'l. v. Mylan Pharm., Inc.*, C.A. No. 1:17-cv-116, 2020 WL 3317105 at *11-13 (N.D. W. Va. June 18, 2020) (on appeal) (invalidity under written description in part on lack of examples discussing data where a POSA would not have expected dose to be effective). Though the district court appeared to credit the patent's title as speaking to the treatment of RRMS and thus informing of the scope of the claims, the title (like the claims) was added many years after the priority date and both were reframed to include RRMS and the 0.5 mg dosage only after the FDA's approval of 0.5 mg Gilenya in the treatment of RRMS. Appx23 (¶52). For years following the priority date Novartis maintained general claims, including kit claims, with no specific dosing of any S1P receptor modulators, let alone fingolimod.

The only information in the patent allegedly driving either the selection of the 0.5 mg daily dosage from the host of dosages disclosed in the hypothetical trial or elsewhere in the specification, or the selection of 0.5 mg as a treatment for

RRMS, are the patent claims themselves – claims that were crafted and presented many years after the June 27, 2006 priority date and long after Novartis tested, and the FDA approved, the 0.5 mg dose of Gilenya. But claims cannot be used to meet the written description requirement – the disclosure must appear in the specification. *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 968 (Fed. Cir. 2002) (rejecting disclosure where "claim language appears in *ipsis verbis* in the specification").

This case is analogous to *Nuvo Pharmaceuticals*, where this Court unequivocally held that if POSAs would not have thought the claimed invention would work nothing in the specification showed that the claimed invention did work, the disclosure failed to support the claims. 923 F.3d at 1381. Accordingly, this Court found the patent invalid based on lack of written description. *Id*. The same result is required here: there is simply nothing to support the district court's findings that a POSA would understand the 0.5 mg dose is an effective treatment for RRMS, particularly where those skilled in the art would not have expected a 0.5 mg dose to treat RRMS and no human had ever been treated with a 0.5 mg dose before the priority date of the '405 patent. And particularly where the inventors never disclosed even once in the specification that their invention was a never-before-seen low-dose of fingolimod to treat RRMS.

B. Inventor and expert testimony confirm that there was no possession of the claimed invention.

In a further effort to shoehorn the claims - which were drafted long after the priority specification was filed and many years after Gilenya was approved - into the specification, the district court looked to the EAE portion of the disclosure. Appx23-26 (¶54-60). Although the EAE experiment reported administration of 0.3 mg/kg weekly dosage in laboratory rats to treat EAE (not RRMS), the district court credited expert testimony that a POSA would have converted the 0.3 mg/kg weekly dose in rats to 0.042 mg/kg daily dose by dividing by 7 – though this is nowhere disclosed in the specification. Appx24 (¶56). Then, the court, crediting expert testimony, found that a POSA would "immediately recognize" that the 0.042 mg/kg daily dose in rats is 60% lower than the lowest known effective dose in prior art—which translated to 0.1 mg/kg daily. Appx24-25 (¶57). Yet again, the lowest known effective dose is nowhere disclosed in the specification.

Nonetheless, fully committed to the pretzel logic proposed by Novartis nearly 14 years post-priority, the court found a POSA would, using a proportionality analysis, determine that since roughly 60% lower than the lowest known effective dose in laboratory rats had proven effective, the same would be true for humans – yet again, absent any disclosure or suggestion in the specification or inventors let alone sound science. Appx25-26 (¶¶58-60). Since the lowest known effective dose in humans was then understood to be 1.25 mg, using

proportionality, the court agreed with Novartis, finding that this would translate to 0.5 mg/daily in humans – all *absent any disclosure in the patent specification*. Appx26 (¶60), Appx23074 (496:12-20), Appx23074-23075 (496:21-497:20), Appx22980-22981 (402:7-403:4).

Nothing in the specification indicates that 1.25 mg was the lowest known effective dose in humans—that conclusion could only come from the results of the Phase II trial of fingolimod in patients with RRMS. Appx25 (¶58), Appx23284 (706:7-17), Appx22692 (114:17-23), Appx23386 (808:2-14). Furthermore, *not a single calculation exists in the specification, and no part of the disclosure tethers—either expressly or impliedly*—any part of *the prophetic example to the EAE animal model*. Appx22824 (246:7-24), Appx22827 (249:13-16), Appx22833-22835 (255:15-257:1), Appx22963 (385:2-17), Appx22824 (246:7-24). This Court has similarly found there is not enough to tie the dosing in a rat model on a weekly basis to dosing in humans on a daily basis, particularly where the 0.5 mg dose is one of many doses and many ranges disclosed. *See e.g. L.A. Biomedical Research Inst. at Harbor-UCLA Med. Ctr. v. Eli Lilly & Co.*, 849 F.3d 1049, 1057-58 (Fed. Cir. 2017) (dosage claims not entitled to priority date where rat study was disclosed and assumptions relating to water intake, weight of rat and human would have had to been made to reach human dose); *see Lockwood v. Am. Airlines, Inc.,* 107 F.3d 1565, 1572 (Fed. Cir. 1997) ("It is not sufficient for purposes of the

written description requirement of § 112 that the disclosure, when combined with the knowledge in the art, would lead one to speculate as to modifications that the *inventor might have envisioned, but failed to disclose.*") (emphasis added); *Idenix Pharm. LLC v. Gilead Sciences, Inc.*, 941 F.3d 1149, 1164 (Fed. Cir. 2019) (invalid where 18 formulas were disclosed as compounds that may treat HCV and no indication the claimed nucleosides could be effective to treat).

Furthermore, although the court credited the mathematical gymnastics proposed by Novartis' experts, those same experts testified that the mathematics they proposed were not actually disclosed. Appx22836 (258:13-19) (Q: "the patent doesn't tell us how they got from the doses that were given to the [rats] to the human once daily." A: ". . . the mathematics are not there"), Appx22829 (251:8-14). Irrespective of the district court's factual findings, expert testimony may not be used to manufacture written description support out of whole cloth, unrelated to the disclosure. *Nuvo Pharm.*, 923 F.3d at 1381 n.4 ("Dispositively, [expert] testimony is irrelevant to the written description inquiry, because it does not point to any disclosure in the specification to which the testimony could relate."); *Hyatt v. Boone*, 146 F.3d 1348, 1353 (Fed. Cir. 1998) (affirming PTAB holding "that witnesses cannot 'establish facts which the disclosure itself should provide'") (quoting *In re Smyth*, 189 F.2d 982, 990 (CCPA 1951)); *Gypsum* 333 U.S. at 396 (finding can be clearly erroneous where testimony conflicts with documents,

testimony given little weight). Yet this is exactly what the district court did.

The expert's litigation-inspired theories are at odds with the inventors' testimony. Although the court found "it appears that the inventors chose the lowest effective dose, which is the once-weekly regimen, for illustration in the prophetic trial," (Appx25-26 (¶59)) this was also based on expert trial testimony. Appx22835-22836 (257:25-258:10). The inventors themselves testified that they had no idea where the hypothetical trial portion of the disclosure came from, that neither had any experience in designing or running clinical trials, and confirmed that there is no disclosure in the '405 patent concerning any conversion of the EAE animal study to human dosing. Appx22929-22930 (351:18-352:17), Appx22893-22894 (316:9-317:24), 22899-22900 (321:19-322:2), Appx22919 (341:11-18). Furthermore, "[a]lthough inventor testimony cannot establish written description support where none exists in the four corners of the specification, *it illuminates the absence of critical description.*" *Nuvo Pharm.*, 923 F.3d at 1381 (emphasis added). Here, inventor testimony highlighted the lack of disclosure for the 0.5 mg dose of fingolimod to treat RRMS and with good reason – low dose fingolimod was not, nor did they understand it to be, their invention. Any invention that might be supported by the specification and by the initial claims would only be geared to S1P modulators in general preventing neo-angiogenesis associated with MS. Appx24736 (1:5-8). And while the disclosure hypothesizes that "S1P receptor

modulators . . . *may be useful in the treatment of one or more of* [RRMS, secondary progressive MS, primary progressive MS and progressive relapsing MS"] *neither the specification nor the original claims provided any specific dosing information for treating RRMS patients*. This was no oversight – the inventors simply had no possession of the '405 patent claims. Appx23075-23076 (497:21-498:3), Appx23119 (541:1-11), Appx23376-23377 (798:1-799:7), Appx23481 (903:3-9), 23478-23480 (900:20-902:12), Appx23482-23483 (904:19-905:9), Appx23119 (541:1-11). Nor should they have had possession since those claim limitations were manufactured years after the priority date and after 0.5 mg Gilenya was first administered to humans and approved by the FDA.

This Court provides guidance on how to determine possession of claims drafted long after the priority filing. The law requires that a specification must provide the "blaze marks necessary to guide a skilled artisan to the claimed invention." *FWP IP APS v. Biogen MA, Inc.*, 749 Fed. App'x 969, 973 (Fed. Cir. 2018); *see also Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1326-27 (Fed. Cir. 2000) ("One cannot disclose a forest in the original application, and then later pick a tree out of the forest and say here is my invention."). Here, there are no "blaze marks" leading to 0.5 mg fingolimod in the treatment of RRMS. More to the point, there is no full, clear, concise, and exact description of 0.5 mg fingolimod in the treatment of RRMS.

If the inventors had invented 0.5 mg daily dosage of fingolimod – e.g., the lowest dosage of fingolimod to treat RRMS, then one would expect "blaze marks" to demonstrate possession. *See FWP IP*, 749 Fed. App'x at 973. Yet there are none. *See Purdue Pharma*, 230 F.3d at 1326-27 (no disclosure where multiple pharmacokinetic parameters were provided with no blaze marks directing the skilled artisan to the claimed value). Furthermore, there is nothing to suggest to one skilled in the art that 0.5 mg daily dose of oral fingolimod is an important defining quality nor does the specification ever indicate a motivation, intent, or otherwise mention any reason to seek the lowest effective dose. *See id.* That requirement was imputed by the district court from expert trial testimony, not based on the '405 patent specification. Appx25-26 (¶59); *Purdue Pharma*, 230 F.3d at 1327-28 (no disclosure where the specification did not disclose that the inventors considered the claimed ratio to be part of their invention). Here, the inventors disclosed exactly what they were in possession of at the time and nothing more – the later addition of a threadbare hypothetical example with multiple possible doses and no anticipated or real results cannot rewrite the entirety of a specification which makes clear that the inventors were exploring (and in possession of) the use of S1P receptor modulators in the treatment or prevention of neo-angiogenesis of MS. If the inventors/Novartis had possessed a working variant of 0.5 mg daily dosage of RRMS, surely the 0.5 mg daily dosage would

have been disclosed as preferred instead of the vast ranges with various dosage regimens provided in the specification. *See Novozymes A/S v. DuPont Nutrition Biosciences APS*, 723 F.3d 1336, 1349 (Fed. Cir. 2013); *see also FWP IP*, 749 Fed. App'x at 973 (rejecting the notion of "picking and choosing to arrive at the claimed invention").

If anything, the specification *leads away* from the 0.5 mg dose. It provides that dosing of S1P receptor modulators will vary depending on "the compound used, the host, the mode of administration and the severity of the condition to be tested." Appx24741 (11:221-24). Large ranges of "preferred daily dosage" of generic S1P receptor modulators are disclosed with unspecific ranges of "about from 0.1 to 100 mg". Appx24741 (11:24-25). The range of daily oral dosages of S1P receptor modulators are disclosed from 0.1 to 50 mg and the only specific dosing of fingolimod indicates that "Compound A [fingolimod] may alternatively be administered intermittently, e.g. at a dose of 0.5 to 3 mg *every other day or once a week*." Appx24741 (11:26-27).

The text of the specification in the '405 patent does not and cannot demonstrate possession of the claimed invention. The claims are invalid for lack of written description.

C. The district court's findings with respect to the hypothetical clinical trial are internally inconsistent, warranting reversal.

Once again, juxtaposing the district court's findings concerning the

prophetic paragraph in the '405 patent specification (which proposed a hypothetical investigation of 0.5 mg, 1.25 mg or 2.5 mg S1P modulator), with the Kappos 2006 abstract (which announced firm plans to investigate fingolimod at 1.25 mg, 0.5 mg and placebo in RRMS patients), exposes irreconcilable inconsistencies in the district court's logic. The district court found that a POSA would *assume* that the 0.5 mg of fingolimod in the hypothetical experiment – which was never conducted and which disclosed several other possible dosages of fingolimod – was an effective treatment. Appx21 (¶49). Yet nothing on the face of the hypothetical example compels this conclusion. No results, anticipated or otherwise are disclosed for any of the listed doses and the hypothetical example proposes only that dosing spans two to six months with patients "remain[ing] on treatment for as long as their disease does not progress and the drug is satisfactorily tolerated." Appx24741 (11:14-16). Nothing compels any conclusion that there will be no disease progression if a patient receives any of the disclosed doses, or even which dose (if any) might yield this result.

Although the court concluded the patent's recitation of 0.5mg in a prophetic example to be effective, somehow the court concluded the exact opposite with regard to Kappos where the district court found a POSA *would not understand* that a 0.5 mg dose was likely to work. Appx30-31 (¶¶75-76). There is simply no way to square these positions: neither the prophetic trial nor the trial disclosed in

Kappos 2006 had been conducted, both were then untested hypothetical scenarios, and no human by mid-2006 had ever been dosed with 0.5 mg of fingolimod. All of this uncertainty – coupled with the widely accepted view in the art that both MS and its treatments were wholly unpredictable - would have made it impossible for a POSA to assume that the 0.5 mg of fingolimod could treat RRMS based on the specification at the time of filing. Appx30 (¶75), Appx15 (¶24). For the court to have concluded otherwise was clear error.

CONCLUSION AND STATEMENT OF RELIEF SOUGHT

The district court committed clear legal and factual errors in holding that the claims of the ’405 patent satisfy the written description requirements of 35 U.S.C. §112, ¶1. The district court judgment upholding the validity of the asserted claims of the ’405 patent—and the resulting injunction—should be reversed. Because the district court correctly found that there is no support whatsoever for “absence an immediately preceding loading dose”, a remand is unnecessary and all claims of the ’405 patent should be invalidated on that basis alone. The district court also erred in finding written description support for the 0.5 mg dose of oral fingolimod. Because the district court’s findings were based on testimony rendered 14 years post-priority and completely untethered to the meager specification, this is a separate basis of invalidity as to each patent claim, warranting reversal.

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ADDENDUM

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NOVARTIS PHARMACEUTICALS CORPORATION, Plaintiff, V. ACCORD HEALTHCARE INC., ET AL., Defendants.	C.A. No. 18-1043-KAJ

ORDER, FINAL JUDGMENT, AND INJUNCTION

WHEREAS, this patent infringement action was brought by Novartis Pharmaceuticals Corporation ("Novartis") alleging, *inter alia*, that Abbreviated New Drug Application ("ANDA") No. 207939, submitted by defendants HEC Pharm Co., Ltd. and HEC Pharm USA Inc. (collectively, "HEC"),[1] infringed claims 1–6 of U.S. Patent No. 9,187,405 (the "'405 Patent"). (*See* D.I. 1.)

WHEREAS, HEC pled defenses and filed declaratory judgment counterclaims against Novartis alleging invalidity and non-infringement of the '405 Patent, (*see* D.I. 134);

WHEREAS, Novartis's actions against all other Defendants in this case have been settled and/or stayed;

WHEREAS, the Court held a four-day bench trial from March 2 to 5, 2020;

WHEREAS, the Court issued its Findings of Facts and Conclusions of Law on August 10, 2020 (D.I. 769); and

[1] Defendant HEC Pharm. Group was previously dismissed from the case. (*See* D.I. 122.)

WHEREAS, the stays against all remaining defendants shall be subject to disposition upon entry of judgment against HEC;

IT IS ORDERED AND ADJUDGED that:

1. Pursuant to Federal Rule of Civil Procedure 54(b), there is no just reason to delay the entry of this Final Judgment against HEC.

2. Final judgment is entered in favor of Novartis and against HEC (1) on Novartis's claims of induced and contributory infringement under 35 U.S.C. § 271(e)(2) of claims 1–6 of the '405 patent by HEC's ANDA No. 207939 and (2) on HEC's defenses and counterclaims of non-infringement and invalidity of claims 1–6 of the '405 patent, and HEC's counterclaims are dismissed with prejudice.

3. Pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any final approval by the United States Food and Drug Administration of HEC's ANDA No. 207939 shall be a date not earlier than the expiration date of the '405 Patent, including any extensions and/or additional periods of exclusivity to that date, except to the extent subsequently (a) agreed between Novartis and HEC or (b) ordered or otherwise permitted by this Court or other tribunal. In the event HEC seeks a stay of the effect of the preceding sentence, HEC shall file and serve a motion to stay by no later than 14 calendar days after entry of this order. Any opposition shall be filed and served no later than 14 calendar days thereafter, and any reply shall be filed and served no later than 7 calendar days after any opposition. All motion papers shall comply with the rules for motions in the Local Rules for the District of Delaware, except that page limits shall be limited as follows: opening and responsive briefs are limited to 10 pages and replies to 5 pages.

4. Pursuant to 35 U.S.C. § 271(e)(4)(B), HEC, its affiliates, subsidiaries, and each of their officers, agents, servants, and employees, those acting in privity or in concert with them, and

any person or entity to whom HEC transfers ANDA No. 207939, are hereby permanently enjoined from engaging in the commercial manufacture, use, offer for sale, and/or sale in the United States and/or importation into the United States of the fingolimod product that is the subject of HEC's ANDA No. 207939 until the expiration date of the '405 Patent, including any extensions and/or additional periods of exclusivity to that date, except to the extent subsequently (a) agreed between Novartis and HEC or (b) ordered or otherwise permitted by this Court or other tribunal.

5. In the event that a party appeals this Final Judgment, any motion for attorneys' fees and/or costs, including any motion that this case is exceptional under 35 U.S.C. § 285, shall be considered timely if filed and served within 60 days after final disposition of any such appeal, and the responding party shall have 60 days after filing and service to respond.

6. In the event that no party appeals this Final Judgment, any motion for attorneys' fees and/or costs, including any motion that this case is exceptional under 35 U.S.C. § 285, shall be considered timely if filed and served within 60 days after the expiration of the time for filing a notice of appeal under Fed. R. App. P. 3 and 4, and the responding party shall have 60 days after filing and service to respond.

7. In the event Novartis seeks exoneration, release, or other relief from the Preliminary Injunction bond entered in this case (D.I. 632), Novartis shall file any such motion by no later than 14 calendar days after entry of this order. Any opposition shall be filed and served no later than 14 calendar days thereafter, and any reply shall be filed and served no later than 7 calendar days after any opposition. All motion papers shall comply with the rules for motions in the Local Rules for the District of Delaware, except that page limits shall be limited as follows: opening and responsive briefs are limited to 10 pages and replies to 5 pages.

IT IS SO ORDERED this 11TH day of September, 2020

Honorable Kent A. Jordan, Third Circuit Judge
Sitting by Designation

Approved as to form and substance:

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NOVARTIS PHARMACEUTICALS CORPORATION, Plaintiff, v. ACCORD HEALTHCARE INC., et al., Defendants.	)	Civil Action No. 18-1043-KAJ **FILED UNDER SEAL**

POST-TRIAL FINDINGS OF FACT AND CONCLUSIONS OF LAW

I. INTRODUCTION

Plaintiff Novartis Pharmaceuticals Corporation ("Novartis") owns Patent No. US 9,187,405 B2 ("the '405 Patent" or "the Patent"), which claims methods to treat Relapsing-Remitting multiple sclerosis ("RRMS") using a compound called "fingolimod," at a daily dosage of 0.5 mg, absent an immediately preceding loading dose. Novartis sells fingolimod under the brand name Gilenya, which the FDA approved in 2010. Defendants HEC Pharm Co., Ltd., HEC Pharm Group, and HEC Pharm USA Inc. (collectively, "HEC") submitted an Abbreviated New Drug Application ("ANDA") to the FDA, seeking approval to make fingolimod 0.5 mg capsules, a generic copy of Novartis's Gilenya product, prior to the expiration of the '405 Patent.[1]

[1] All other defendants in this case have settled with Novartis.

Novartis then brought this suit, alleging that HEC's ANDA infringes the '405 Patent. HEC, of course, disputes that. It claims that its label does not instruct physicians to omit a loading dose from the dosing regimen, so it is not practicing one of the elements of the patent claims in suit.

HEC also brought a counterclaim that the '405 Patent is invalid for lack of written description and anticipation. As to written description, HEC claims that the Patent has no written description for the negative limitation "absent an immediately preceding loading dose" or for the claimed 0.5mg daily dose. And concerning anticipation, HEC argues that the '405 Patent is anticipated by an abstract published in the Journal of Neurology and presented at the European Neurologic Society Meeting in 2006. Novartis responds that the Patent specification provides the necessary written description and that the abstract does not anticipate because it is not prior art, does not disclose the claimed invention, and is not enabled.

The parties presented their cases during a four-day bench trial from March 2-5, 2020. As explained below, I conclude that HEC is liable for contributory and induced infringement because the label for its generic version of Gilenya instructs physicians to perform each limitation in the asserted claims of the Patent. I further conclude that the Patent is not invalid. The Patent contains an adequate written description, and it was not anticipated by the abstract. The following are my findings of fact and conclusions of law.

II. FINDINGS OF FACT

A. The Parties and the Patent

1. Plaintiff Novartis is a corporation organized and existing under the laws of Delaware, having a principal place of business at 1 Health Plz, East Hanover, New Jersey 07936. (D.I. 715, Pretrial Order ("PTO") Ex. 1 ¶ 1.)

2. Defendant HEC Pharm Co., Ltd. is a corporation organized and existing under the laws of China, having a principal place of business at Binjiang Road 62, Yidu, Yichang, 443300, Hubei, China. Defendant HEC Pharm USA Inc. is a corporation organized and existing under the laws of New Jersey, having a principal place of business at 116 Village Blvd, Suite 200, Princeton, NJ 08540. (*Id.* ¶¶ 2-3.) As noted in the Introduction, *supra*, HEC Pharm Co., Ltd., HEC Pharm USA Inc., and HEC Pharm Group are referred to collectively herein as "HEC."

3. Novartis owns the '405 Patent, which claims methods to treat RRMS with 0.5 mg of fingolimod daily absent an immediately preceding loading dose. (JTX-001.) The claims of the '405 Patent, all of which are asserted in this case, are as follows:

    1. A method for reducing or preventing or alleviating relapses in Relapsing-Remitting multiple sclerosis in a subject in need thereof, comprising orally administering to said subject 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol, in free form or in a pharmaceutically acceptable salt form, at a daily dosage of 0.5 mg, absent an immediately preceding loading dose regimen.

2. The method according to claim 1 wherein 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride is administered.

3. A method for treating Relapsing-Remitting multiple sclerosis in a subject in need thereof, comprising orally administering to said subject 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol, in free form or in a pharmaceutically acceptable salt form, at a daily dosage of 0.5 mg, absent an immediately preceding loading dose regimen.

4. The method according to claim 3 wherein 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride is administered.

5. A method for slowing progression of Relapsing-Remitting multiple sclerosis in a subject in need thereof, comprising orally administering to said subject 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol, in free form or in a pharmaceutically acceptable salt form, at a daily dosage of 0.5 mg, absent an immediately preceding loading dose regimen.

6. The method according to claim 5 wherein 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride is administered.

(JTX-001 at 12:48-13:10.)

4. The specification describes an example of the claimed dosing regimen in a prophetic human clinical trial ("the Prophetic Trial"), where RRMS patients receive fingolimod "at a daily dosage of 0.5" mg for at least two to six months. (*Id.* at 11:8-14.) There is

no mention of a loading dose. (*Id.*) A prophetic trial is a study that is described on paper but not actually performed. (Tr. at 734:1-736:2.) Because FDA-approved clinical trials take a long time to perform, prophetic trials are sometimes used in patent applications to explain "if the drug were effective [in humans at a dose observed to be effective in animals], how you administer it, at what dose, and how you would follow the patient on that dose to understand whether clinical benefit was being achieved." (*Id.* at 735:2-6.)

5. The specification also describes the results of an Experimental Autoimmune Encephalomyelitis experiment ("EAE" experiment). (JTX-001 at 10:32-11:2.) In the EAE experiment, disease that mimics RRMS is induced in laboratory animals called Lewis rats, with "an acute disease within 11 days, followed by an almost complete remission around day 16 and a relapse at around days 26." (*Id.* at 10:35-39.) The specification says that 0.3 mg/kg of fingolimod, given once a week, "completely inhibits the relapse phases[.]" (*Id.* at 10:62-11:2.)

6. Novartis sells fingolimod under the brand name Gilenya, which the FDA approved in 2010. Fingolimod hydrochloride is Gilenya's sole active ingredient, at a recommended dose of 0.5 mg daily administered orally in a capsule. (D.I. 715, PTO Ex. 1 ¶ 15.)

7. HEC submitted ANDA No. 207939 to the FDA under the provisions of 21 U.S.C. § 355(j), seeking approval to engage in the commercial manufacture, use, offer for

sale, sale, and/or importation of Fingolimod 0.5 mg capsules, a generic copy of Novartis's Gilenya product, prior to the expiration of the '405 Patent. (*Id.* ¶ 17.)

8. HEC's proposed prescribing information states in the "Dosage and Administration" section of the proposed label submitted with HEC's ANDA that "[i]n adults, the recommended dosage of fingolimod capsule is 0.5 mg orally once-daily." HEC's proposed prescribing information states in the "Indications and Usage" section that "[f]ingolimod capsules are indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in patients 18 years of age and older." (*Id.* ¶¶ 19-20.)

9. Chief Judge Leonard P. Stark presided over this case before it was reassigned to me. He adopted a definition of a person of ordinary skill in the art ("POSA") which is "'a multi-disciplinary research team' that includes '1) a Ph.D. with expertise in the area of neurology and/or an M.D. having several years of clinical experience treating multiple sclerosis patients, and who would be knowledgeable about the multiple sclerosis literature,' and '2) a pharmacologist with experience in drug development.'" (*Id.* ¶ 33.)

10. He also construed the claim preambles ("A method for reducing or preventing or alleviating relapses in Relapsing-Remitting multiple sclerosis in a subject in need thereof, comprising …" (Claim 1); "A method for treating Relapsing-Remitting

multiple sclerosis in a subject in need thereof, comprising …" (Claim 3); and "A method for slowing progression of Relapsing Remitting multiple sclerosis in a subject in need thereof, comprising …" (Claim 5)) to be a limiting statement of purpose. (D.I. 561 at 5.)

11. He construed the term "daily dosage of 0.5 mg" as the amount of drug that someone takes in a given day. (*Id.* at 9.)

12. I have reviewed those conclusions and fully adopt them here.

B. The Witnesses

1. Dr. Fred Lublin, Ph.D.

13. Dr. Fred Lublin, testifying for Novartis, is a neurologist specializing in MS at the Mount Sinai Medical Center in New York. (Tr. at 107:23-108:7.) Dr. Lublin has been an MS physician for over 40 years, has treated several thousand patients during that time, and continues to treat numerous patients. (*Id.* at 108:18-109:1.) He has published over 200 peer-reviewed publications, the vast majority of which relate to MS or animal models of that disease. (*Id.* at 109:2-13.) Dr. Lublin has been involved in many MS clinical trials for various MS medications. (*Id.* at 110:17-24.)

14. Dr. Lublin was involved in the clinical trials for fingolimod. (*Id.* at 112:13-15.) He was a member of the data safety monitoring board for the Phase I trial and a member

of the advisory committee for the Phase III protocols.[2] (*Id.* at 112:16-20.) He spent approximately 18 years working on the fingolimod clinical trial. (*Id.* at 112:21-23.)

15. At trial, Dr. Lublin was received as an "expert medical doctor specializing in MS and the design [and] execution [of] clinical trials." (*Id.* at 112:24-113:5.)

2. Peter Hiestand (via deposition)

16. Peter Hiestand is one of the named inventors, along with Christian Schnell, on the '405 Patent. (*Id.* at 314:6-15.) Hiestand and Schnell collaborated on the EAE experiment described in the Patent. (*Id.* at 315:3-6, 315:21-316:7.)

17. They "were the first ones to provide proof that the compound will work at 0.5 mg, which, … was not known at the time to the persons arranging Phase III trials." (*Id.* at 332:13-17.) Hiestand and Schnell translated the low effective EAE doses they observed to the lower human dose of 0.5 mg through a proportionality analysis. (*Id.* at 319:9-321:18.)

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[2] Clinical trials are conducted in phases. A Phase I trial involves a small number of people and is studied over a short period of time to test safety and dosing. (Tr. 123:10-15.) A Phase II trial "is called a proof-of-concept study." (*Id.* at 123:23-25.) It involves more participants and lasts longer than a Phase I trial. (*Id.* at 124:1-4.) The researchers in Phase II are still assessing safety and dosing but are also assessing whether a drug may be effective. (*Id.* at 123:25-124:7.) Phase III trials "are called pivotal trials. They involve larger numbers of patients, usually over a thousand; longer periods time …. They have to have a clinical endpoint as the primary outcome measure." (*Id.* at 128:19-129:4.) "[I]f you succeed in Phase III, you usually can take that data to someone like the FDA to try and license a drug." (*Id.* at 129:5-7.)

3. Christian Schnell (via deposition)

18. Christian Schnell is one of the named inventors on '405 Patent. (*Id.* at 338:4-7.) He was involved in the EAE experiments that underlie the Patent. (*Id.* at 339:1-341:4.)

4. Peter Waibel (via deposition)

19. Peter J. Waibel is in-house legal counsel for Novartis and was deposed pursuant to Federal Rule of Civil Procedure 30(b)(6) as a designated witness for Novartis. (*Id.* at 353:17-354:1.)

5. Dr. Robert Fujinami, Ph.D.

20. Dr. Robert Fujinami, testifying for HEC, is a Professor in the Department of Pathology, the Vice Dean for Faculty and Academic Affairs for the University of Utah School of Medicine and is the Assistant Vice President for Academic Affairs for University of Utah Health. (*Id.* at 378:2-10.) Dr. Fujinami obtained his Ph.D. from Northwestern University and then received post-doctoral training at the Scripps Research Institute. (*Id.* at 378:25-379:9.)

21. Dr. Fujinami's primary field of research is in EAE and related immunological mechanisms that affect initiation, exacerbations, or remissions in preclinical animal models for multiple sclerosis. (*Id.* at 378:11-19.) He has experience conducting EAE experiments using Lewis rats and other animal models. (*Id.* at 379:19-380:2.)

22. At trial, Dr. Fujinami was received as an expert, as a Ph.D. with expertise in the area of neurology. (*Id.* at 382:2-8, 383:4-9.)

6. Dr. Peter Calabresi, M.D. (via deposition)

23. Dr. Peter Calabresi is an MS physician, researcher, and professor of neurology at Johns Hopkins. (*Id.* at 423:25-424:19.) He regularly treats MS patients. (*Id.* at 424:20-425:13.) He has been a principal investigator on several multiple sclerosis clinical trials. (*Id.* at 425:14-427:16.) He was the principal investigator for the fingolimod U.S. Phase III trial called "FREEDOMS II." (*Id.*) He was also on the "FREEDOMS I" steering committee, and assisted with study design, including dose selection. (*Id.* at 428:4-429:10.)

24. Dr. Calabresi explained that clinical investigators "enter into a clinical trial with . . . equipoise, where you don't really know in the beginning what the answer is going to be, and that's the reason for doing the clinical trial." (*Id.* at 428:16-429:10.) Phase III clinical trials, "or some arms" thereof, sometimes fail (*id.* 429:11-25), and the Phase III fingolimod investigators entered into that phase with "equipoise" about the 0.5 mg dose (*id.* at 437:16-22).

7. Dr. Radojka Savic, Ph.D.

25. Dr. Radojka Savic, testifying for HEC, is an Associate Professor of Bioengineering & Therapeutic Sciences in the School of Pharmacy and an Associate Professor of Pulmonary and Critical Care in the Department of Medicine at the University of California, San Francisco. (*Id.* at 466:16-467:1.) Dr. Savic obtained her Ph.D. in Pharmacometrics from the School of Pharmacy at Uppsala University in Sweden. (*Id.*

at 463:24-464:4.) After obtaining her Ph.D., Dr. Savic did post-doctoral training in biostatistics and pharmacometrics at the French Institute for Health, INSERM in Paris, France and clinical pharmacology at the School of Medicine at Stanford University. (*Id.* at 464:23-465:9.) At the same time, Dr. Savic maintained her status as a researcher in pharmacometrics at Uppsala University, where she was responsible for the entire program of modeling disease progression and PK/PD relationships in several large multiple sclerosis clinical studies for the multiple sclerosis drug Cladribine. (*Id.* at 465:10-21.)

26. At trial, Dr. Savic was received as an expert in clinical pharmacology, including developing dosing regimens between animal and human models, and in clinical trials. (*Id.* at 471:22-472:3.)

8. <u>Dr. Paul Hoffman, M.D.</u>

27. Dr. Paul Hoffman, testifying for HEC, is a senior scientist in the Department of Neurology at the University of Florida's College of Medicine and at University of Florida Health, the clinical arm of the medical school. (*Id.* at 516:15-21.) Prior to that, Dr. Hoffman worked in the Department of Veteran's Affairs for 35 years, retiring in 2015. (*Id.* at 520:12-17.) Dr. Hoffman's experience includes being a researcher in EAE, reviewing clinical trials, and having over 40 years of experience treating multiple sclerosis patients. (*Id.* at 516:15-522:3; 532:12-533:13.)

28. At trial, Dr. Hoffman was received as an expert medical doctor with particular expertise in the treatment of multiple sclerosis. (*Id.* at 525:9-526:3.)

9. Dr. Shreeram Aradhye (via deposition)

29. Dr. Shreeram Aradhye was, at the time of his deposition, the Chief Medical Officer of Novartis and, during 2003 to 2005, he was the medical lead on the first Phase III trial of fingolimod in transplant patients and the Phase III RRMS trial of fingolimod. (*Id.* at 646:16-22.)

10. Dr. Lawrence Steinman, M.D.

30. Dr. Lawrence Steinman, testifying for Novartis, is an MS physician and researcher, and a Professor of Neurology at Stanford University. (*Id.* at 684:2-8.) Dr. Steinman earned his medical degree from Harvard University in 1973, and subsequently studied under the inventor of the MS drug Copaxone®. (*Id.* at 686:3-12.) Dr. Steinman has treated over 4,000 MS patients, and has prescribed Gilenya many times. (*Id.* at 684:11-21.) He leads a laboratory at Stanford (*id.* at 685:3-5), the institution where he has been conducting MS drug research since 1975 (*id.* at 686:13-15). Research in Dr. Steinman's laboratory led to the development of an FDA-approved treatment for MS marketed as Tysabri® (natalizumab). (*Id.* at 686:16-21.)

31. Dr. Steinman also has extensive experience with the EAE model: he has conducted approximately 1,000 EAE experiments over the last 45 years (*id.* at 693:10-693:21), and has used both acute and relapsing EAE models (*id.* at 693:22-694:4). Dr.

Steinman has published over 500 peer-reviewed publication related to MS or EAE (*id.* at 685:6-12) and is the named inventor on approximately 50 patents (*id.* at 687:15-18).

32. Dr. Steinman has been involved with MS clinical trials, serving in a variety of roles, including as principal investigator and as a member of data safety monitoring boards and advisory boards. (*Id.* at 686:22-687:6.) He has advised companies on the design of clinical trials since the 1980s. (*Id.* at 687:7-14.)

33. At trial, Dr. Steinman was received as an "expert medical doctor with expertise in multiple sclerosis and drug development … including clinical trials." (*Id.* at 688:17-689:1.)

11. Dr. William Jusko, Ph.D.

34. Dr. William Jusko, testifying for Novartis, is a distinguished professor of pharmaceutical sciences at the University of Buffalo. Dr. Jusko specializes in pharmacology, and focuses on pharmacokinetics and pharmacodynamics, in particular with respect to immunosuppressants. (*Id.* at 845:12-846:14.) Dr. Jusko has published over 600 publications in peer-reviewed journals, and has been the editor-in-chief of the primary journal in his field, the Journal of Pharmacokinetics and Pharmacodynamics. (*Id.* at 846:15-847:1.) He has also received prestigious awards in the field of pharmacology. (*Id.* at 847:2-13.)

35. Dr. Jusko's laboratory has conducted pharmacokinetic and pharmacodynamics modeling and analyses for pharmaceutical companies developing immunosuppressant drugs, including for Novartis on fingolimod. (*Id.* at 848:8-24.) Dr. Jusko's studies on fingolimod involved developing complex models for fingolimod in monkeys and rats. (*Id.* at 849:7-850:22.)

36. At trial, Dr. Jusko was received as an expert in pharmacology. (*Id.* at 852:10-17.)

C. Infringement

37. HEC's ANDA included a certification that the '405 Patent is invalid, unenforceable, and/or will not be infringed by HEC's generic fingolimod product. (D.I. 715, PTO Ex. 1 ¶ 21.)

38. HEC's proposed label is materially identical to the label for Gilenya. (PTX-310; Tr. 221:8-22.)

39. HEC's proposed label instructs doctors to perform the '405 Patent's claimed methods for the purposes stated in the preambles of the claims. Those purposes are in Sections 1 and 14 of HEC's proposed label. (Tr. 223:3-225:22.)

40. With respect to the preambles of claims 1 and 5 of the Patent, HEC's product is, according to the proposed label, "indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include … relapsing-remitting disease[.]" (PTX-310.0005; Tr. 224:3-15.) The label also describes clinical trials showing the 0.5 mg dose reduced annualized relapse rates and slowed disability progression. (PTX-310.0027-

29; Tr. 224:16-225:15, 642:17-643:10.) Reducing relapses and slowing progression are the only two clinical benefits described in HEC's proposed label. (Tr. 224:16-225:2, 642:17-643:16.) The label describes those benefits when summarizing the Phase III clinical trials for RRMS. (*Id.*) Dr. Hoffman testified that he prescribes Gilenya to patients solely for the purposes described in the label's clinical trial section. (*Id.* 643:17-23.)

41. With respect to the preamble of claim 3, again, HEC's ANDA product is, according to the proposed label, "for the treatment of patients with relapsing forms of multiple sclerosis (MS), to include … relapsing remitting disease[.]" (PTX-310.0005.)

42. The Patent's claims all require the administration of 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol, which is the chemical name for fingolimod. (JTX-001, col. 12-13.) Section 11 of HEC's proposed label instructs that doctors are administering and patients are taking the drug compound fingolimod hydrochloride, and that is as claimed in the '405 Patent. (PTX-310.0020.)

43. The claims require "orally administering … [fingolimod] . . . at a daily dosage of 0.5 mg." (JTX-001, col. 12-13.) HEC's proposed label instructs that "the recommended dosage … is 0.5 mg orally once daily[.]" (PTX-310.0006; Tr. 227:2-230:7.) That is the only dose the label recommends. (Tr. 640:14-20.) Any other dose would be off-label. (*Id.* 229:17-230:4.) Other ANDA documents from HEC show that only 0.5 mg – and no more – is the recommended dose. (PTX-273.0001; Tr. 228:6-22.)

44. A loading dose is a "greater-than-normal dose that you usually use at the start of a therapy to … jump-start the levels [of a drug] in the body." (Tr. 201:13-16.) HEC's proposed label does not mention a loading dose. (*Id.* at 641:16-22.)

45. Nothing in HEC's proposed label says to prescribe anything more or less than 0.5 mg, and the label provides a caution that there is "a greater incidence of adverse reactions without additional benefit" for doses over 0.5 mg. (PTX-310.0006.)

46. Dr. Hoffman agreed that it would be very unusual to administer a loading dose with fingolimod for an off-label use. (Tr. 547:12-549:2.)

47. Dr. Lublin has prescribed Gilenya to hundreds of patients and has never given Gilenya with a loading dose. (*Id.* at 220:15-18, 230:5-7.)

48. Dr. Hoffman testified that the only clinical benefits for HEC's generic version of Gilenya would be those identified in the clinical trial section of the proposed label. (*Id.* at 642:17-643:23.) Those trials used a dose of 0.5 mg daily, without a loading dose, solely in RRMS patients. (*Id.* at 130:7-22; PTX-310.0027.)

D. Invalidity

1. Written Description

49. A person of skill in the art would understand that the Patent describes a daily dosage of 0.5 mg of fingolimod without a preceding loading dose. A person of skill would understand that the Prophetic Trial in the Patent assumes that the daily dosage of 0.5 mg is an effective treatment, and that the first dose listed in the example is the 0.5 mg

daily dose. (Tr. 753:22-754:21.) The Prophetic Trial describes how a person of skill would investigate clinical benefit in patients receiving treatment, i.e. the daily 0.5 mg dose, by seeing the patient, doing neurologic exams, and following the disease with, for instance, magnetic resonance imaging. (*Id.* at 754:22-755:22.) The Prophetic Trial describes the methods persons of skill would use to keep track of patients receiving treatment. (*Id.* at 755:23-756:15.)

50. A person of skill would understand the Prophetic Trial to disclose a method of treatment because it specifies that the purpose of the daily dose is treatment and describes how a person of skill would follow a patient for that treatment. (*Id.* at 753:22-754:15, 804:1-805:10; 863:22-864:18.) Dr. Lublin explained that the Prophetic Trial discloses a treatment purpose because subjects "initially … received treatment for two to six months" and then "remain on treatment for as long as their disease does not progress[.]" (JTX-001 11:13-14; Tr. at 233:23-235:5.) There is no placebo group. (Tr. at 235:1-5.)

51. Dr. Lublin explained that while the Prophetic Trial described in the Patent specification was not actually conducted, it provides anticipated results from treatment. (*Id.* at 242:22-243:20.) While the Prophetic Trial would be insufficient for "purposes of the FDA," (*id.* at 267:10-13), patents are viewed from "the purview of a person of ordinary skill" (*id.* at 235:13-235:18), and can be valid and enforceable

according to the terms of title 35 of the United States Code, even if other regulatory requirements may exist for approval of the drug covered by the patent in question.

52. Read as a whole, the Patent tells a person of ordinary skill in the art that the invention is about treating RRMS. (*Id.* at 858:20-861:2.) The title indicates that it speaks of a treatment for RRMS. (*Id.* at 860:5-8.) The abstract also mentions that the drug could be used to treat conditions such as multiple sclerosis. (*Id.* at 860:11-13, 20.) Dr. Hoffman agreed that the title and specification of the '405 Patent tell persons of ordinary skill in the art that the invention is about using S1P receptor modulators, including fingolimod, for treating RRMS. (*Id.* at 597:2-10, 619:16-620:6.)

53. The two examples, animal and human, are "complementary" when read together in the context of the entire Patent. (*Id.* at 864:19-24.) Dr. Lublin testified that the Prophetic Trial shows a treatment purpose because, "when you read the patent, . . . in the animal experiment they said we've got it; a lower dose of fingolimod will work. They … make the conversion to human dosing, and then they show this clinical trial and that they're treating it. That's how I read the patent." (*Id.* at 235:19-236:8.)

54. A person of skill would understand that the inventors used a relapsing EAE model. The section of the '405 Patent reporting the experimental results is "In Vivo: Relapsing Experimental Autoimmune Encephalomyelitis (EAE)." (JTX-001.0007 at 10:32-33.) Dr. Hoffman agrees that a person of skill would understand the EAE example to describe a relapsing model, not an acute model. (Tr. 625:19-626:4,

627:15-629:10.) A person of skill would understand the inhibition of relapses could be achieved by any of the dosing schedules described in the EAE example, including the 0.3 mg/kg per week dose. (*Id.* at 629:19-630:16.)

55. A person of skill would understand that the Lewis rat animal model is a good model for relapsing EAE. (*Id.* at 838:9-840:19; *see also* 324:23-325:15.) A person of skill would also understand that EAE was the dominant model for studying MS treatments, and that results in EAE were reasonably correlated to results in humans. (*Id.* at 776: 10-13, 639:10-12; PTX-095.001.)

56. The EAE experimental results set forth in the Patent report an effective dose of 0.3 mg/kg weekly. (JTX-001 at 11:2.) According to Dr. Steinman, a person of skill in the art would have converted the 0.3 mg/kg weekly dose to 0.042 mg/kg daily, in order to compare the daily dose with the lowest known effective daily dose. (Tr. at 747:6-748:19.) Dr. Jusko explained that dividing by 7 to go from a weekly to a daily dose is appropriate because fingolimod has a very long half-life, distributes extensively, and stays in brain tissue for a long time. (*Id.* at 865:12-24, 904:2-904:18.) The method for equalizing exposure between single and multiple doses is well understood and straightforward since the dynamics of lymphocyte suppression were known to be slow. (*Id.* at 866:18-867:4.)

57. According to Dr. Jusko, when reading the EAE experimental results reported in the Patent, a person of skill would immediately recognize that 0.3 mg/kg weekly (0.042

mg/kg daily) in rats is lower than the lowest known effective dose in the prior art (0.1 mg/kg daily). (*Id.* at 862:25-863:21.) It is approximately 60% lower. (Id. at 865:23-24.)

58. A person of skill would understand that the EAE results in the '405 Patent therefore demonstrate that a proportionally lower dose (again, roughly 60% lower) could be effective in humans. (*Id.* at 865:4-867:4, 902:17-907:8.) It was understood from the results of the Phase II trial of fingolimod in patients with RRMS that the lowest known effective dose in humans was 1.25 mg daily. (*Id.* at 706:7-17, 114:17-23.) A 60% lower dose is the 0.5 mg dose described in the Patent. (*Id.*) According to Dr. Jusko, "[w]ith the extensive studies done in the animal model, the appreciable information of some of the pharmacokinetics and some of the pharmacodynamics of humans, the two systems [– animal and human –] were highly in agreement." (*Id.* at 866:10-14.)

59. Dr. Steinman agrees that a person of ordinary skill in the art would understand that the inventors translated the lowest dose that had ever been seen as effective from their EAE experiment (0.3 mg/kg once per week) to the 0.5 dose. (*Id.* at 778:25-779:14.) The Prophetic Trial would confirm to a person of skill that the inventors did a translation from their EAE experiments to the 0.5 mg daily dose in humans, as exemplified in the Patent. (*Id.* at 865:25-866:9.) It appears that the inventors chose

the lowest effective dose, which is the once-weekly regimen, for illustration in the Prophetic Trial. (*Id.* at 257:25-258:10.)

60. A person of skill would understand that the inventors were in possession of the claimed method, based on their innovative EAE experiments, understanding of the mechanism of action, using a well-established model, and the correlation to humans due to "extensive studies done with fingolimod between animals and humans." (*Id.* at 870:20-871:3.)

61. There was no recitation of a loading dose in the specification. (*Id.* at 766:16-767:2.) The Prophetic Trial describes the dosing regimen (dosage, frequency, and length) and does not involve a loading dose. (*Id.* at 214:10-215:11.) The absence of an immediately preceding loading dose from the specification, and from the Prophetic Trial, would tell a person of skill that loading doses are excluded from the invention.

62. The Prophetic Trial describes giving a "daily dosage of 0.5 . . . mg" fingolimod to treat RRMS, started "initially." (JTX-001 at 11:8-13.) The Prophetic Trial tells a person of skill that on day 1, treatment begins with a daily dose of 0.5 mg, not a loading dose. (Tr. at 765:5-766:2.) If a loading dose were directed, the Patent would say that a loading dose should be administered "initially." (*Id.* at 756:16-757:8 ("[I]t was zero out of two places where they . . . necessarily would have put it in."); *id.* at 863:22-864:18 ("They specified [an] initial regimen that does not include a loading dose.").)

63. A loading dose is necessarily a higher-than-daily dose. (*Id.* at 766:4-766:6.) On this record, starting with a daily dose plainly implies that there is no loading dose. (*Id.* at 766:7-15.) Dr. Hoffman agreed that a loading dose is usually given "as the first dose[.]" (*Id.* at 547:12-18.)

64. The EAE example discloses a dosing regimen which does not involve a loading dose. (*Id.* at 767:3-5; 215:16-21.) Dr. Hoffman, testifying for HEC, agreed. (*Id.* at 631:18-22.)

65. The Patent describes alternative dosing regimens, like "intermittent dosing," but does not describe loading doses. (*Id.* at 617:12-617:23.)

66. A person of skill in 2006 would not expect a loading dose to be used to treat RRMS with fingolimod. (*Id.* at 548:2-549:2, 551:6-12.)

2. Anticipation

67. The abstract published in the Journal of Neurology and presented at the European Neurologic Society Meeting in 2006, *Design of a randomized, placebo-controlled study of oral fingolimod (FFTY720) in relapsing-remitting multiple sclerosis* ("Kappos 2006"), and dated Mary 27-31, 2006, does not anticipate the Patent. (DTX-047; Tr. 186:2-9.) Kappos 2006 announces an upcoming Phase III trial of 1.25 mg and 0.5 mg doses of fingolimod daily compared to a placebo. (DTX-009.)

68. First, there is insufficient evidence to establish Kappos 2006 as prior art, as it has not been shown to have been available before June 27, 2006.[3] A copy of Kappos 2006 with a declaration from an employee from the British Library was offered but not admitted into evidence. The declaration is inadmissible hearsay and, in any event, is internally inconsistent regarding the location and availability of the document. (Tr. at 372:15-16; DTX-009.) The library stamp on the cover of the journal refers to a "Document Supply Centre," while the declaration refers instead to a "reading room." (Tr. at 367:23-370:21; DTX-009.)

69. The declarant, Rupert Lee, was not present at trial and not available for deposition. His declaration states that his "knowledge of the records and record keeping practices and procedures of the Library [] relies to some extent on information collated by a third party." (DTX-9.00001; *see also* Tr. at 369:20-370:6.) Mr. Lee admits that he

[3] The parties agree that June 2006 is the relevant time period for when prior art had to be publicly available in order to anticipate the patent. (*Compare* Tr. 43:25-44:2, 44:13-14, *with* Tr. 984:2-7, *and* 813:6-8.) The inventors filed a patent application in Great Britain on June 27, 2006. A Patent Cooperation Treaty application was filed on June 25, 2007. That application was translated and filed in the United States Patent and Trademark Office as U.S. Serial No. 12/303,765 (the "'765 Application"). The '405 Patent is a division of U.S. Application No. 13/149,468, filed on May 31, 2011, which is a continuation of the '765 Application. (D.I. 715, PTO Ex. 1 ¶ 13.) Based on the pre-America Invents Act 35 U.S.C. § 102(b), HEC says that publications are prior art only if published more than a year before the United States filing, so June 25, 2006. (D.I. 748 at 3.) Novartis says that the priority date, and thus the relevant date to determine if a document is prior art, is when the patent was filed in Great Britain – June 27, 2006. (D.I. 758 at 28.) For purposes of analysis, I can accept either June 25 or June 27, 2006 as the relevant date. Despite HEC advocating for June 25, it appears that June 27 is the more favorable date for HEC.

was not involved in the cataloging process for Kappos 2006, and his declaration was made 12 years after the event. (DTX-9.00001-00002.)

70. Mr. Lee does not provide any information on the procedures for cataloging, indexing, or shelving. For instance, there is no information about: (1) the cataloging process; (2) what happens to a reference once it is cataloged; (3) how the reference gets to a publicly accessible location; (4) who was responsible for carrying out such procedures; (5) how long such procedures would have taken; (6) how the reference would have been identified or indexed in a reading room; (7) how the existence of the reference would have been made known to the public; (8) how an interested person would search for the reference. (DTX-009.)

71. No evidence was admitted that shows that Kappos 2006 was publicly accessible prior to June 27, 2006. Although witnesses testified that it is typical that such abstracts are printed in advance of the meeting and in conjunction with a presentation at the meeting, there was no testimony verifying that this abstract was actually publicly available or that it accompanied a presentation.[4] (Tr. at 441:2-442:8; 672:9-673:5.)

72. Kappos 2006 was separately admitted into evidence, without the British Library declaration, as DTX-047. The abstract describes a "study of oral fingolimod

[4] Although Dr. Aradhye said that the abstract was prepared "in anticipation" of the meeting at which it was presented, (Tr. at 672:19-24,) that does not say when it became publicly available, nor does Dr. Calabresi's acknowledgement that abstracts are published in conjunction with meetings.

(FTY720) in relapsing-remitting multiple sclerosis[.]" (DTX-47.00001-00002.) It suggests three test groups, with dosing levels at 1.25 mg, 0.5 mg, and placebo, in a "randomized, double-blind" study. (DTX-47.00002-00003.)

73. Kappos 2006 does not describe a treatment for RRMS, but rather articulates a test or drug trial. (Tr. at 240:21-23.) To a person of ordinary skill in the art, "[t]esting is not treating." (*Id.* at 175:25-176:1.) The abstract offers no evidence of effectiveness, which a person of skill would look for as an indication of a treatment purpose. (*Id.* at 176:24-177:9.) The inclusion of a placebo group, which involves no treatment of RRMS, further demonstrates that the abstract describes a trial with unknown results. (*Id.* at 176:24-177:9; 895:11-896:5.)

74. Kappos 2006 does not mention a loading dose. (*Id.* at 674:9-11; 894:10-12.) Unlike a patent, which is presumed complete, an abstract of an academic paper is not presumed to contain all of the necessary information about the study. (*Id.* at 204:16-205:1; 897:1-3.) The failure to mention a loading dose does not, therefore, indicate that the dose was not present in the trial, but only that the presence or absence of a loading dose was not mentioned in the abstract. (*Id.* at 896:18-898:10.)

75. Kappos 2006 does not enable the use of 0.5 mg daily to treat RRMS because it would require undue experimentation. (*Id.* at 210:11-212:13.) "MS is a rather unpredictable disease which makes studying it all the more difficult." (*Id.* at 211:25-212:1.)

Kappos does not contain any data, like an EAE study, to indicate that a lower dosage of fingolimod would work in the treatment of RRMS. (*Id.* at 212:9-13.)

76. The prior art did not tell a person of ordinary skill that a dose of 0.5 mg was likely to work. It was known in the literature that, for a drug to be effective, it has to achieve a certain level of lymphocyte depletion, and that "the dose-response relationship is very steep[,]" meaning that, if the dose was not high enough, the drug would provide no benefit. (*Id.* at 891:10-892:6.)

III. CONCLUSIONS OF LAW

A. Infringement

1. Under the Hatch-Waxman Act, "[i]t shall be an act of infringement to submit an [ANDA] . . . for a drug . . . the use of which is claimed in a patent, . . . if the purpose of such submission is to obtain approval . . . to engage in the commercial manufacture, use, or sale of a drug . . . before the expiration of such patent." 35 U.S.C. § 271(e)(2)(A).

2. "[T]he substantive determination whether actual infringement or inducement will take place is determined by traditional patent infringement analysis, just the same as it is in other infringement suits[,]" including those under 35 U.S.C. §§ 271(a)-(c). *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1365 (Fed. Cir. 2003).

3. "[A] patentee seeking relief under § 271(e)(2) must prove by a preponderance of the evidence that what is to be sold will infringe." *Id.* at 1366 (internal quotation marks and citations omitted).

4. Any physician following and prescribing fingolimod according to HEC's proposed label will directly infringe.

1. Induced Infringement

5. "Whoever actively induces infringement of a patent shall be liable as an infringer." 35 U.S.C. § 271(b). "To prove induced infringement, the patentee must show direct infringement, and that the alleged infringer knowingly induced infringement and possessed specific intent to encourage another's infringement." *Toshiba Corp. v. Imation Corp.*, 681 F.3d 1358, 1363 (Fed. Cir. 2012) (internal quotation marks omitted). In the ANDA context, in which the accused product is not yet on the market, the patentee only need show infringement will occur in the future. *Warner-Lambert Co.*, 316 F.3d at 1365-66.

6. The content of the accused infringer's proposed product label controls the induced infringement inquiry, and "[t]he pertinent question is whether the … label instructs users to perform the patented method." *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010). "The mere existence of direct infringement by physicians, while necessary to find liability for induced infringement, is not sufficient

for inducement." *Takeda Pharm. U.S.A., Inc. v. West-Ward Pharm. Corp.*, 785 F.3d 625, 631 (Fed. Cir. 2015).

7. "FDA regulations provide guidance on how to interpret a label." *BTG Int'l Ltd. v. Amneal Pharm. LLC*, 352 F. Supp. 3d 352, 391 (D.N.J. 2018). Pursuant to such regulations, the label must contain complete instructions on dosing and administration. *See* 21 C.F.R. 201.57.

8. "[W]here a product has substantial noninfringing uses, intent to induce infringement cannot be inferred even when the alleged inducer has actual knowledge that some users of its product may be infringing the patent." *AstraZeneca*, 633 F.3d at 1059 (Fed. Cir. 2010) (internal quotation marks and alterations omitted). "Evidence of active steps … taken to encourage direct infringement, such as advertising an infringing use or instructing how to engage in an infringing use, show[s] an affirmative intent that the product be used to infringe[.]" *Metro-Goldwyn-Mayer Studios Inc. v. Grokster, Ltd.*, 545 U.S. 913, 936 (2005) (internal quotation marks and citation omitted).

9. HEC is liable for induced infringement. HEC's proposed label instructs the user to perform every element of the patented method, demonstrating knowing inducement. (*See* Findings of Fact ("FF") ¶¶ 40-48.) The prescribing physician would understand the label to contain the complete dosing information, and the instructions dictate the dose of the drug in question exactly as in the Patent – 0.5 mg daily without a loading

dose. (*See* FF ¶¶ 43-48.) If a user follows the instructions, there will be direct infringement. Instructing use that will infringe is an active step that demonstrates a specific intent to infringe.

2. Contributory Infringement

10. As pertinent here, contributory infringement is found where: (1) there is direct infringement; (2) the accused infringer had knowledge of the patent at issue; and (3) the product has no substantial non-infringing uses. *Lucent Techs., Inc. v. Gateway, Inc.*, 580 F.3d 1301, 1320 (Fed. Cir. 2009); 35 U.S.C. § 271(c).

11. Unlike induced infringement, the mental state required for contributory infringement is mere knowledge of infringement, not necessarily intent to cause infringement. *Lifetime Indus., Inc. v. Trim-Lok, Inc.*, 869 F.3d 1372, 1381 (Fed. Cir. 2017).

12. "A noninfringing use is substantial when it is not unusual, far-fetched, illusory, impractical, occasional, aberrant, or experimental." *Gruenthal GMBH v. Alkem Labs. Ltd.*, 919 F.3d 1333, 1340 (Fed. Cir. 2019) (citations and internal quotation marks omitted). "In a pharmaceutical case, the noninfringing use must be in accordance with the use for which the product is indicated." *Id.*

13. The patentee must make a prima facie showing that a product is not "suitable for substantial non-infringing use[.]" *Golden Blount, Inc. v. Robert H. Peterson Co.*, 438 F.3d 1354, 1363 (Fed. Cir. 2006). Once the patentee makes out a prima facie case,

the burden of production shifts to the accused infringer to introduce evidence to demonstrate otherwise. *Id.* at 1363-64.

14. HEC is liable for contributory infringement. HEC knew of the '405 Patent and the treatment method it sets forth. (*See* FF ¶¶ 38-40.) Because the only uses for HEC's generic fingolimod product are those identified in the clinical trial section of the proposed label, there is no substantial non-infringing use for which the product is indicated. (*See* FF ¶¶ 40-43.) If a user follows the instructions on the label, there will be direct infringement.

B. Invalidity

15. "A patent is presumed to be valid, and this presumption only can be overcome by clear and convincing evidence to the contrary." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1354 (Fed. Cir. 2010) (en banc) (internal quotation marks and citations omitted).

16. "[T]he party challenging the patent bears the burden of proving invalidity by clear and convincing evidence." *Takeda Pharm. Co. v. Zydus Pharm. USA, Inc.*, 743 F.3d 1359, 1366 (Fed. Cir. 2014).

17. The Patent, which was filed in Great Britain in June 2006 and in the United States in June 2007 (FF ¶ 68 & n.3), is subject to the pre-America Invents Act ("AIA") standards for testing validity. *See* Leahy-Smith America Invents Act, Pub. L. No. 112–29, 125 Stat. 284, 293 (2011) (providing that the amendments made by the Act

do not take effect until 18 months after the enactment of the Act, i.e. March 16, 2013, and apply to any application for patent, and to any patent issuing thereon, that has an effective filing date after that date); 35 U.S.C. § 100(i)(B) (defining the effective filing date as the priority date).

18. The only invalidity arguments advanced by HEC are (1) that the '405 Patent has an insufficient written description for the no-loading-dose limitation and for the claimed 0.5 mg daily dose; and (2) that the '405 Patent is anticipated by the Kappos 2006 reference.

1. Written Description

19. Under 35 U.S.C. § 112(a), the specification of a patent "shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention."

20. "[T]he test for sufficiency [of a written description] is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad,* 598 F.3d at 1351 (internal citation and quotation marks omitted).

21. "[T]he test requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art." *Id.* at 1351.

22. The factors to consider "for evaluating the adequacy of the" written description include "the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, [and] the predictability of the aspect at issue." *Id.* (quoting *Capon v. Eshhar*, 418 F.3d 1349, 1359 (Fed. Cir. 2005)).

23. A person of ordinary skill in the art "is deemed to read the words used in the patent documents with an understanding of their meaning in the field, and to have knowledge of any special meaning and usage in the field." *Multiform Desiccants, Inc. v. Medzam, Ltd.*, 133 F.3d 1473, 1477 (Fed. Cir. 1998).

24. The Patent here provides a sufficient written description of the invention such that a person of ordinary skill would know that the inventors were in possession of the invention. Read as a whole, the Patent describes a daily dosage of 0.5 mg of fingolimod, without a preceding loading dose, to treat RRMS. (*See* FF ¶¶ 49-66.) A person of ordinary skill would understand that the invention contained a treatment purpose, and that the treatment is for RRMS. (*See* FF ¶¶ 50-55.) The EAE model and the Prophetic Trial demonstrate a dosage of 0.5 mg per day, a lower dosage of fingolimod than existed in the prior art. (*See* FF ¶¶ 56-60.) The EAE model and the

Prophetic Trial also both indicate to a person of ordinary skill that the claimed invention did not include the administration of a loading dose. (*See* FF ¶¶ 61-66.)

2. **Anticipation**

25. Pre-AIA 35 U.S.C. § 102(b) states that "[a] person shall be entitled to a patent unless … the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country more than one year prior to the date of the application for patent in the United States…" 35 U.S.C. § 102 (b) (2002).

26. Here, the Patent Cooperation Treaty application was filed on June 25, 2007, (FF ¶ 68 & n.3,) so any publications that pre-date June 25, 2006, are prior art to the claims of the '405 Patent under 35 U.S.C. § 102(b).[5]

1. HEC Has Not Met Its Burden to Prove Kappos 2006 Is Prior Art

27. "Whether an asserted anticipatory document qualifies as a 'printed publication' under § 102 is a legal conclusion based on underlying factual determinations." *Cooper Cameron Corp. v. Kvaerner Oilfield Prods., Inc.*, 291 F.3d 1317, 1321 (Fed. Cir. 2002). To qualify as a printed publication under § 102(b), the publication must be publicly accessible. *Jazz Pharm., Inc. v. Amneal Pharm., LLC*, 895 F.3d 1347, 1355 (Fed. Cir. 2018). "Public accessibility is a question of fact[.]" *Id.* at 1356.

[5] As stated in footnote 3, *supra*, the parties disagree about the date for analyzing what constitutes prior art. Even if I accept the later date of June 27, 2006, it does not matter to the analysis.

28. To be publicly accessible, the reference must be "cataloged or indexed in a meaningful way." *In re Cronyn*, 890 F.2d 1158, 1161 (Fed. Cir. 1989).

29. Hearsay is not admissible as proof of a fact unless it falls under a hearsay exception. Fed. R. Evid. 802. The residual exception to the hearsay bar provides that a hearsay statement may be admitted, even if it does not meet any other hearsay exceptions, if it "is supported by sufficient guarantees of trustworthiness" and is more probative than other pieces of evidence. Fed. R. Evid. 807. The residual hearsay exception is to be used sparingly. *United States v. Bailey*, 581 F.2d 341, 347 (3d Cir. 1978).

30. The Lee declaration was offered for the truth of the matter asserted therein and therefore is hearsay. It does not fit within one of the recognized exceptions to the rule against hearsay, nor it is supported by "sufficient guarantees of trustworthiness" to be admissible under the residual hearsay exception. Lee was not present at trial and not available for deposition, so Novartis had no opportunity to probe the trustworthiness and facts surrounding the Lee declaration. (FF ¶ 69.) The Lee declaration does not provide any information on the procedures for cataloging, indexing, or shelving and was created 12 years after the cataloging. (FF ¶¶ 69-70.)

31. HEC failed to show by clear and convincing evidence that Kappos 2006 was publicly available in June 2006 or earlier. HEC has not presented any evidence, let alone clear and convincing evidence, of how Kappos 2006 was cataloged, and so has not met its

burden to show that the reference was publicly available in June 2006 or earlier.[6] (FF ¶¶ 68-71.) HEC similarly has not shown that Kappos 2006 was otherwise publicly available. Testimony that HEC points to (*see* n.4, *supra*) certainly does not constitut clear and convincing evidence of public accessibility.

2. Even if Kappos 2006 Was Prior Art, It Does Not Anticipate the Claims of the Patent

32. "A patent is invalid for anticipation if a single prior art reference discloses each and every limitation of the claimed invention." *Schering Corp. v. Geneva Pharm.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003).

33. "Moreover, a prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference." *Id.*

34. "A reference may anticipate inherently if a claim limitation that is not expressly disclosed is necessarily present, or inherent, in the single anticipating reference." *In re Montgomery*, 677 F.3d 1375, 1379-80 (Fed. Cir. 2012) (citations and internal quotation marks omitted). "The inherent result must inevitably result from the

[6] HEC's waiver argument is not well-founded, as pointed out by Novartis. In Novartis's pretrial statement of contested facts, Novartis says that HEC bears the burden of proof that the asserted prior art references are actually prior art to the '405 patent. (D.I. 715, PTO Ex. 2 ¶ 5.) In its pretrial submission, under the heading "Statement of Issues of Fact that Remain to be Litigated[,]" HEC listed one of those issues as whether Kappos 2006 is prior art. (*Id.* Ex. 3 ¶ 59.)

disclosed steps; [i]nherency ... may not be established by probabilities or possibilities." *Id.* (citations and internal quotation marks omitted).

35. "[A] patent claim cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled.'" *Verizon Servs. Corp. v. Cox Fibernet Va., Inc.*, 602 F.3d 1325, 1337 (Fed. Cir. 2010) (internal quotation marks and citations omitted). To be "enabled," a reference must enable one of skill in the art to make and use the invention without undue experimentation. *In re Wands*, 858 F.2d 731, 736-37 (Fed. Cir. 1988).

36. "Factors to be considered in determining whether a disclosure would require undue experimentation … include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." *Id.* at 737.

37. HEC has failed to prove by clear and convincing evidence that Kappos 2006 discloses the no-loading-dose limitation. (FF ¶¶ 72, 74.) Kappos 2006 is a short abstract and does not preclude the use of a loading dose in the clinical trial it described. (FF ¶¶ 72, 74.)

38. HEC has also failed to prove that Kappos 2006 discloses the purpose limitations of the preambles. (FF ¶ 73.) Chief Judge Stark held that the claim preambles are a

limiting statement of purpose, and that the Patent is "directed toward and limited to treating MS[.]" (D.I. 561 at 8 & n.3.). Kappos 2006, on the other hand, discloses a test. A person of skill would not have read Kappos 2006 as disclosing a treatment for RRMS. As Kappos 2006 describes only an early-stage clinical trial, it is too theoretical to be enabled. (FF ¶¶ 73, 75-76.)

IV. SUMMARY OF CONCLUSIONS

For the reasons set forth herein, HEC is liable for induced and contributory infringement of the '405 Patent, and the '405 Patent is not invalid for lack of written description or anticipation. Accordingly, judgment will be entered in favor of Novartis and against HEC.

Kent A. Jordan, Circuit Judge
Sitting by designation

August 10, 2020
Wilmington, Delaware

US009187405B2

(12) **United States Patent**
Hiestand et al.

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(54) **S1P RECEPTOR MODULATORS FOR TREATING RELASPING-REMITTING MULTIPLE SCLEROSIS**

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(51) **Int. Cl.**

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A61K 31/137	(2006.01)
A61K 31/397	(2006.01)

(52) **U.S. Cl.**

CPC ***C07C 215/08*** (2013.01); ***A61K 31/137*** (2013.01); ***A61K 31/397*** (2013.01); *A61K 31/13* (2013.01)

(58) **Field of Classification Search**

CPC A61K 31/13; A61K 31/137
USPC 514/667, 903
See application file for complete search history.

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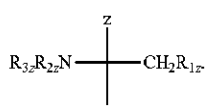
(57) **ABSTRACT**

The present invention relates uses of an S1P receptor modulator such as 2-substituted 2-amino-propane-1,3-diol or 2-amino-propanol derivatives, e. g. a compound comprising a group of formula X



for the treatment or prevention of neo-angiogenesis associated with a demyelinating disease, e.g. multiple sclerosis.

6 Claims, No Drawings

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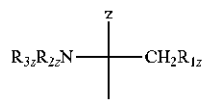
S1P RECEPTOR MODULATORS FOR TREATING RELASPING-REMITTING MULTIPLE SCLEROSIS

The present invention relates to the use of an S1P receptor modulator in the treatment or prevention of neo-angiogenesis associated with a demyelinating disease, e.g. multiple sclerosis.

S1 P receptor modulators are typically sphingosine analogues, such as 2-substituted 2-amino-propane-1,3-diol or 2-amino-propanol derivatives, e. g. a compound comprising a group of formula X.

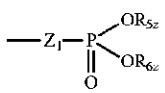
Sphingosine-1 phosphate (hereinafter "S1P") is a natural serum lipid. Presently there are eight known S1P receptors, namely S1P1 to S1P8. S1 P receptor modulators are typically sphingosine analogues, such as 2-substituted 2-amino-propane-1,3-diol or 2-amino-propanol derivatives, e. g. a compound comprising a group of formula X

(X)



wherein Z is H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, phenyl, phenyl substituted by OH, C_{1-6}alkyl substituted by 1 to 3 substituents selected from the group consisting of halogen, C_{3-8}cycloalkyl, phenyl and phenyl substituted by OH, or CH_2—R_{4z} wherein R_{4z} is OH, acyloxy or a residue of formula (a)

(a)



wherein Z_1 is a direct bond or O, preferably O;

each of R_{5z}, and R_{6z}, independently, is H, or C_{1-4}alkyl optionally substituted by 1, 2 or 3 halogen atoms;

R_{1z} is OH, acyloxy or a residue of formula (a); and each of R_{2z} and R_{3z} independently, is H, C_{1-4}alkyl or acyl.

Group of formula X is a functional group attached as a terminal group to a moiety which may be hydrophilic or lipophilic and comprise one or more aliphatic, alicyclic, aromatic and/or heterocyclic residues, to the extent that the resulting molecule wherein at least one of Z and R_{1z} is or comprises a residue of formula (a), signals as an agonist at one of more sphingosine-1-phosphate receptor.

S1P receptor modulators are compounds which signal as agonists at one or more sphingosine-1 phosphate receptors, e.g. S1P1 to S1P8. Agonist binding to a S1P receptor may e.g. result in dissociation of intracellular heterotrimeric G-proteins into Gα-GTP and Gβγ-GTP, and/or increased phosphorylation of the agonist-occupied receptor and activation of downstream signaling pathways/kinases.

The binding affinity of S1P receptor modulators to individual human S1P receptors may be determined in following assay:

S1P receptor modulator activities of compounds are tested on the human S1P receptors $S1P_1$, $S1P_2$, $S1P_3$, $S1P_4$ and $S1P_5$. Functional receptor activation is assessed by quantifying compound induced GTP [γ-^{35}S] binding to membrane protein prepared from transfected CHO or RH7777 cells stably expressing the appropriate human S1P receptor. The assay technology used is SPA (scintillation proximity based assay). Briefly, DMSO dissolved compounds are serially diluted and added to SPA-bead (Amersham-Pharmacia) immobilised S1P receptor expressing membrane protein (10-20 μg/well) in the presence of 50 mM Hepes, 100 mM NaCl, 10 mM $MgCl_2$, 10 μM GDP, 0.1% fat free BSA and 0.2 nM GTP [γ-^{35}S] (1200 Ci/mmol). After incubation in 96 well microtiterplates at RT for 120 min, unbound GTP [γ-^{35}S] is separated by a centrifugation step. Luminescence of SPA beads triggered by membrane bound GTP [γ-^{35}S] is quantified with a TOPcount plate reader (Packard). EC_{50}s are calculated using standard curve fitting software. In this assay, the S1P receptor modulators preferably have a binding affinity to S1P receptor <50 nM.

Preferred S1P receptor modulators are e.g. compounds which in addition to their S1P binding properties also have accelerating lymphocyte homing properties, e.g. compounds which elicit a lymphopenia resulting from a re-distribution, preferably reversible, of lymphocytes from circulation to secondary lymphatic tissue, without evoking a generalized immunosuppression. Nave cells are sequestered; CD4 and CD8 T-cells and B-cells from the blood are stimulated to migrate into lymph nodes (LN) and Peyer's patches (PP).

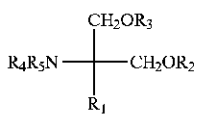
The lymphocyte homing property may be measured in following Blood Lymphocyte Depletion assay:

A S1P receptor modulator or the vehicle is administered orally by gavage to rats. Tail blood for hematological monitoring is obtained on day −1 to give the baseline individual values, and at 2, 6, 24, 48 and 72 hours after application. In this assay, the S1P receptor agonist or modulator depletes peripheral blood lymphocytes, e.g. by 50%, when administered at a dose of e.g. <20 mg/kg.

Examples of appropriate S1P receptor modulators are, for example:

Compounds as disclosed in EP627406A1, e.g. a compound of formula I

I



wherein R_1 is a straight- or branched (C_{12-22}) chain

which may have in the chain a bond or a hetero atom selected from a double bond, a triple bond, O, S, NR_6, wherein R_6 is H, C_{1-4}alkyl, aryl-C_{1-4}alkyl, acyl or (C_{1-4} alkoxy)carbonyl, and carbonyl, and/or

which may have as a substituent C_{1-4}alkoxy, C_{2-4}alkenyloxy, C_{2-4}alkynyloxy, arylC_{1-4}alkyl-oxy, acyl, C_{1-4}alkylamino, acylamino, (C_{1-4}alkoxy)carbonyl, (C_{1-4}alkoxy)-carbonylamino, acyloxy, (C_{1-4}alkyl) carbamoyl, nitro, halogen, amino, hydroxyimino, hydroxy or carboxy; or

R_1 is

a phenylalkyl wherein alkyl is a straight- or branched (C_{6-20})carbon chain; or

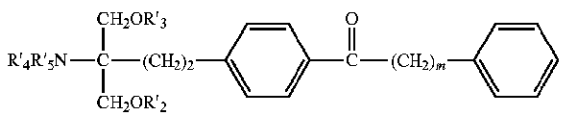
a phenylalkyl wherein alkyl is a straight- or branched (C_{1-30})carbon chain wherein said phenylalkyl is substituted by

a straight- or branched (C_{6-20})carbon chain optionally substituted by halogen,

a straight- or branched (C_{6-20})alkoxy chain optionally substitued by halogen,

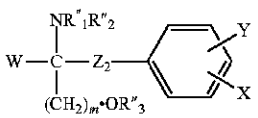
a straight- or branched (C_{6-20})alkenyloxy,
phenyl-C_{1-14}alkoxy, halophenyl-C_{1-4}alkoxy, phenyl-C_{1-14} alkoxy-C_{1-14}alkyl, phenoxy-C_{1-4}alkoxy or phenoxy-C_{1-4} alkyl,
cycloalkylalkyl substituted by C_{6-20}alkyl,
heteroarylalkyl substituted by C_{6-20}alkyl,
heterocyclic C_{6-20}alkyl or
heterocyclic alkyl substituted by C_{2-20}alkyl,
and wherein
the alkyl moiety may have
in the carbon chain, a bond or a heteroatom selected from a double bond, a triple bond, O, S, sulfinyl, sulfonyl, or NR_6, wherein R_6 is as defined above, and
as a substituent C_{1-4}alkoxy, C_{2-4}alkenyloxy, C_{2-4}alkynyloxy, arylC_{1-4}alkyloxy, acyl, C_{1-4}alkylamino, C_{1-4}alkylthio, acylamino, (C_{1-4}alkoxy)carbonyl, (C_{1-4}alkoxy) carbonylamino, acyloxy, (C_{1-4}alkyl)carbamoyl, nitro, halogen, amino, hydroxy or carboxy, and
each of R_2, R_3, R_4 and R_5, independently, is H, C_{1-4} alkyl or acyl
or a pharmaceutically acceptable salt or hydrate thereof;
Compounds as disclosed in EP 1002792A1, e.g. a compound of formula II

II



wherein m is 1 to 9 and each of R'_2, R'_3, R'_4 and R'_5, independently, is H, C_{1-6}alkyl or acyl,
or a pharmaceutically acceptable salt or hydrate thereof;
Compounds as disclosed in EP0778263 A1, e.g. a compound of formula III

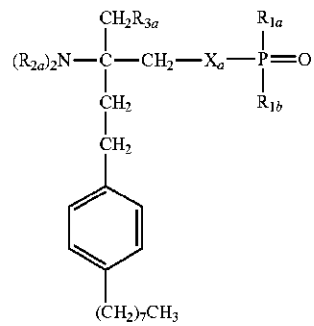
III



wherein W is H; C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl; unsubstituted or by OH substituted phenyl; $R''_4O(CH_2)_n$; or C_{1-6}alkyl substituted by 1 to 3 substituents selected from the group consisting of halogen, C_{3-8}cycloalkyl, phenyl and phenyl substituted by OH;
X is H or unsubstituted or substituted straight chain alkyl having a number p of carbon atoms or unsubstituted or substituted straight chain alkoxy having a number (p-1) of carbon atoms, e.g. substituted by 1 to 3 substitutents selected from the group consisting of C_{1-6}alkyl, OH, C_{1-6}alkoxy, acyloxy, amino, C_{1-6}alkylamino, acylamino, oxo, haloC_{1-6}alkyl, halogen, unsubstituted phenyl and phenyl substituted by 1 to 3 substituents selected from the group consisting of C_{1-6}alkyl, OH, C_{1-6}alkoxy, acyl, acyloxy, amino, C_{1-6}alkylamino, acylamino, haloC_{1-6}alkyl and halogen; Y is H, OH, C_{1-6}alkoxy, acyl, acyloxy, amino, C_{1-6}alkylamino, acylamino, haloC_{1-6}alkyl or halogen, Z_2 is a single bond or a straight chain alkylene having a number or carbon atoms of q,
each of p and q, independently, is an integer of 1 to 20, with the proviso of $6 \le p+q \le 23$, m' is 1, 2 or 3, n is 2 or 3,

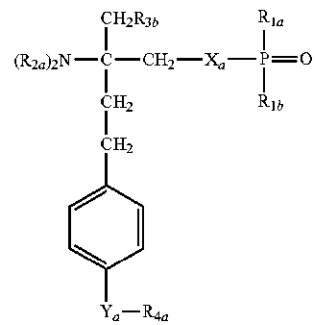
each of R''_1, R''_2, R''_3 and R''_4, independently, is H, C_{1-4}alkyl or acyl,
or a pharmaceutically acceptable salt or hydrate thereof,
Compounds as disclosed in WO02/18395, e.g. a compound of formula IVa or IVb

IVa



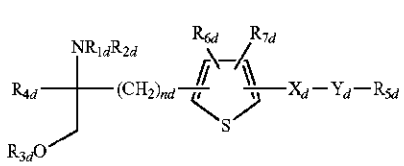
or

IVb



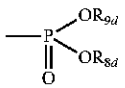
wherein X_a is O, S, NR_{1a} or a group $—(CH_2)_{na}—$, which group is unsubstituted or substituted by 1 to 4 halogen; n_a is 1 or 2, R_{1a} is H or (C_{1-4})alkyl, which alkyl is unsubstituted or substituted by halogen; R_{1a} is H, OH, (C_{1-4})alkyl or O(C_{1-4})alkyl wherein alkyl is unsubstituted or substituted by 1 to 3 halogen; R_{1b} is H, OH or (C_{1-4})alkyl, wherein alkyl is unsubstituted or substituted by halogen; each R_{2a} is independently selected from H or (C_{1-4})alkyl, which alkyl is unsubstituted or substituted by halogen; R_{3a} is H, OH, halogen or O(C_{1-4})alkyl wherein alkyl is unsubstituted or substituted by halogen; and R_{3b} is H, OH, halogen, (C_{1-4})alkyl wherein alkyl is unsubstituted or substituted by hydroxy, or O(C_{1-4})alkyl wherein alkyl is unsubstituted or substituted by halogen; Y_a is $—CH_2—$, —C(O)—, —CH(OH)—, —C(=NOH)—, O or S, and R_{4a} is (C_{4-14})alkyl or (C_{4-14})alkenyl;
or a pharmaceutically acceptable salt or hydrate thereof;
Compounds as disclosed in WO02/06268AI, e.g. a compound of formula V

V



wherein each of R_{1d} and R_{2d}, independently, is H or an amino-protecting group;

R_{3d} is hydrogen, a hydroxy-protecting group or a residue of formula



R_{4d} is C_{1-4}alkyl;

n_d is an integer of 1 to 6;

X_d is ethylene, vinylene, ethynylene, a group having a formula -D-CH_2— (wherein D is carbonyl, —CH(OH)—, O, S or N), aryl or aryl substituted by up to three substitutents selected from group a as defined hereinafter;

Y_d is single bond, C_{1-10}alkylene, C_{1-10}alkylene which is substituted by up to three substitutents selected from groups a and b, C_{1-10}alkylene having O or S in the middle or end of the carbon chain, or C_{1-10}alkylene having O or S in the middle or end of the carbon chain which is substituted by up to three substituents selected from groups a and b;

R_{5d} is hydrogen, C_{3-6}cycloalkyl, aryl, heterocyclic group, C_{3-6}cycloalkyl substituted by up to three substituents selected from groups a and b, aryl substituted by up to three substituents selected from groups a and b, or heterocyclic group substituted by up to three substituents selected from groups a and b;

each of R_{6d} and R_{7d}, independently, is H or a substituent selected from group a;

each of R_{8d} and R_{9d}, independently, is H or C_{1-4}alkyl optionally substituted by halogen;

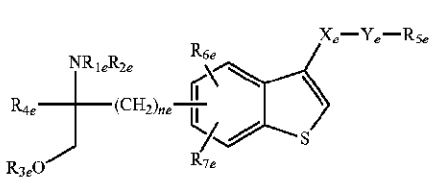
<group a> is halogen, lower alkyl, halogeno lower alkyl, lower alkoxy, lower alkylthio, carboxyl, lower alkoxycarbonyl, hydroxy, lower aliphatic acyl, amino, mono-lower alkylamino, di-C_{1-4}alkylamino, acylamino, cyano or nitro; and

<group b> is C_{3-6}cycloalkyl, aryl or heterocyclic group, each being optionally substituted by up to three substituents selected from group a;

with the proviso that when R_{5d} is hydrogen, Y_d is a either a single bond or linear C_{1-10} alkylene, or a pharmacologically acceptable salt, ester or hydrate thereof;

Compounds as disclosed in JP-14316985 (JP2002316985), e.g. a compound of formula VI

VI

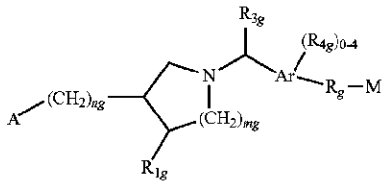


wherein R_{1e}, R_{2e}, R_{3e}, R_{4e}, R_{5e}, R_{6e}, R_{7e}, n_e, X_e and Y_e are as disclosed in JP-14316985;

or a pharmacologically acceptable salt, ester or hydrate thereof;

Compounds as disclosed in WO03/062252A1, e.g. a compound of formula VII

VII



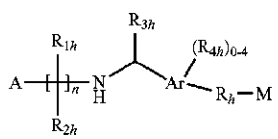
wherein

Ar is phenyl or naphthyl; each of m_g and n_g independently is 0 or 1; A is selected from COOH, PO_3H_2, PO_2H, SO_3H, PO(C_{1-3}alkyl)OH and 1H-tetrazol-5-yl; each of R_{1g} and R_{2g} independently is H, halogen, OH, COOH or C_{1-4}alkyl optionally substituted by halogen; R_{3g} is H or C_{1-4}alkyl optionally substituted by halogen or OH; each R_{4g} independently is halogen, or optionally halogen substituted C_{1-4}alkyl or C_{1-3}alkoxy; and each of R_g and M has one of the significances as indicated for B and C, respectively, in WO03/062252A1;

or a pharmacologically acceptable salt, solvate or hydrate thereof;

Compounds as disclosed in WO 03/062248A2, e.g. a compound of formula VIII

VIII

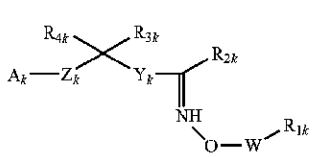


wherein Ar is phenyl or naphthyl; n is 2, 3 or 4; A is COOH, 1H-tetrazol-5-yl, PO_3H_2, PO_2H_2, —SO_3H or PO(R_{5h})OH wherein R_{5h} is selected from C_{1-4}alkyl, hydroxyC_{1-4}alkyl, phenyl, —CO—C_{1-3}alkoxy and —CH(OH)-phenyl wherein said phenyl or phenyl moiety is optionally substituted; each of R_{1h} and R_{2h} independently is H, halogen, OH, COOH, or optionally halogeno substituted C_{1-6}alkyl or phenyl; R_{3h} is H or C_{1-4}alkyl optionally substituted by halogen and/OH; each R_{4h} independently is halogeno, OH, COOH, $S(O)_{0,\ 1\ or\ 2}C_{1-3}$alkyl, C_{1-3}alkoxy, C_{3-6}cycloalkoxy, aryl or aralkoxy, wherein the alkyl portions may optionally be substituted by 1-3 halogens; and each of R_h and M has one of the significances as indicated for B and C, respectively, in WO03/062248A2

or a pharmacologically acceptable salt, solvate or hydrate thereof.

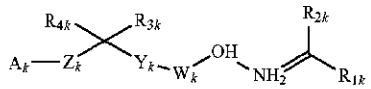
Compounds as disclosed in WO 04/103306A, WO 05/000833, WO 05/103309 or WO 05/113330, e.g. compounds of formula IXa or IXb

IXa



-continued

IXb



wherein

A_k is $COOR_{5k}$, $OPO(OR_{5k})_2$, $PO(OR_{5k})_2$, SO_2OR_{5k}, $POR_{5k}OR_{5k}$ or 1H-tetrazol-5-yl, R_{5k} being H or C_{1-6}alkyl;

W_k is a bond, C_{1-3}alkylene or C_{2-3}alkenylene;

Y_k is C_{6-10}aryl or C_{3-9}heteroaryl, optionally substituted by 1 to 3 radicals selected from halogen, OH, NO_2, C_{1-6}alkoxy; halo-substituted C_{1-6}alkyl and halo-substituted C_{1-6}alkoxy;

Z_k is a heterocyclic group as indicated in WO 04/103306A, e.g. azetidine;

R_{1k} is C_{6-10}aryl or C_{3-9}heteroaryl, optionally substituted by C_{1-6}alkyl, C_{6-10}aryl, C_{6-10}arylC_{1-4}alkyl, C_{3-9}heteroaryl, C_{3-9}heteroarylC_{1-4}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-4}alkyl, C_{3-8}heterocycloalkyl or C_{3-8}heterocycloalkylC_{1-4}alkyl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R_{1k} may be substituted by 1 to 5 groups selected from halogen, C_{1-6}alkyl, C_{1-6}alkoxy and halo substituted-C_{1-6}alkyl or -C_{1-6}alkoxy;

R_{2k} is H, C_{1-6}alkyl, halo substituted C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl: and

each of R_{3k} or R_{4k}, independently, is H, halogen, OH, C_{1-6}alkyl, C_{1-6}alkoxy or halo substituted C_{1-6}alkyl or C_{1-6}alkoxy;

and the N-oxide derivatives thereof or prodrugs thereof,

or a pharmacologically acceptable salt, solvate or hydrate thereof.

The compounds of formulae I to IXb may exist in free or salt form. Examples of pharmaceutically acceptable salts of the compounds of the formulae I to VI include salts with inorganic acids, such as hydrochloride, hydrobromide and sulfate, salts with organic acids, such as acetate, fumarate, maleate, benzoate, citrate, malate, methanesulfonate and benzenesulfonate salts, or, when appropriate, salts with metals such as sodium, potassium, calcium and aluminium, salts with amines, such as triethylamine and salts with dibasic amino acids, such as lysine. The compounds and salts of the combination of the present invention encompass hydrate and solvate forms.

Acyl as indicated above may be a residue R_y—CO— wherein R_y is C_{1-6}alkyl, C_{3-6}cycloalkyl, phenyl or phenyl-C_{1-4} alkyl. Unless otherwise stated, alkyl, alkoxy, alkenyl or alkynyl may be straight or branched.

Aryl may be phenyl or naphthyl, preferably phenyl.

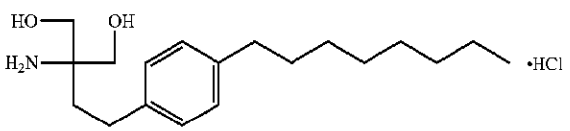
When in the compounds of formula I the carbon chain as R_1 is substituted, it is preferably substituted by halogen, nitro, amino, hydroxy or carboxy. When the carbon chain is interrupted by an optionally substituted phenylene, the carbon chain is preferably unsubstituted. When the phenylene moiety is substituted, it is preferably substituted by halogen, nitro, amino, methoxy, hydroxy or carboxy.

Preferred compounds of formula I are those wherein R_1 is C_{13-20}alkyl, optionally substituted by nitro, halogen, amino, hydroxy or carboxy, and, more preferably those wherein R_1 is phenylalkyl substituted by C_{6-14}-alkyl chain optionally substituted by halogen and the alkyl moiety is a C_{1-6}alkyl optionally substituted by hydroxy. More preferably, R_1 is phenyl-C_{1-6}alkyl substituted on the phenyl by a straight or branched, preferably straight, C_{6-14}alkyl chain. The C_{6-14}alkyl chain may be in ortho, meta or para, preferably in para.

Preferably each of R_2 to R_5 is H.

In the above formula of V "heterocyclic group" represents a 5- to 7 membered heterocyclic group having 1 to 3 heteroatoms selected from S, O and N. Examples of such heterocyclic groups include the heteroaryl groups indicated above, and heterocyclic compounds corresponding to partially or completely hydrogenated heteroaryl groups, e.g. furyl, thienyl, pyrrolyl, azepinyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, 1,2,3-oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyranyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, pyrrolidinyl, pyrrolyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl or pyrazolidinyl. Preferred heterocyclic groups are 5- or 6-membered heteroaryl groups and the most preferred heterocyclic group is a morpholinyl, thiomorpholinyl or piperidinyl group.

A preferred compound of formula I is 2-amino-2-tetradecyl-1,3-propanediol. A particularly preferred S1P receptor agonist of formula I is FTY720, i.e. 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol in free form or in a pharmaceutically acceptable salt form (referred to hereinafter as Compound A), e.g. the hydrochloride salt, as shown:



A preferred compound of formula II is the one wherein each of R'_2 to R'_5 is H and m is 4, i.e. 2-amino-2-{2-[4-(1-oxo-5-phenylpentyl)phenyl]ethyl}propane-1,3-diol, in free form or in pharmaceutically acceptable salt form (referred to hereinafter as Compound B), e.g. the hydrochloride.

A preferred compound of formula III is the one wherein W is CH_3, each of $R"_1$ to $R"_3$ is H, Z_2 is ethylene, X is heptyloxy and Y is H, i.e. 2-amino-4-(4-heptyloxyphenyl)-2-methylbutanol, in free form or in pharmaceutically acceptable salt form (referred to hereinafter as Compound C), e.g. the hydrochloride. The R-enantiomer is particularly preferred.

Compounds may be in phosphorylated form. A preferred compound of formula IVa is the FTY720-phosphate (R_{2a} is H, R_{3a} is OH, X_a is O, R_{1a} and R_{1b} are OH). A preferred compound of formula IVb is the Compound C-phosphate (R_{2a} is H, R_{3b} is OH, X_a is O, R_{1a} and R_{1b} are OH, Y_a is O and R_{4a} is heptyl). A preferred compound of formula V is Compound B-phosphate.

A preferred compound of formula VI is (2R)-2-amino-4-[3-(4-cyclohexyloxybutyl)-benzo[b]thien-6-yl]-2-methylbutan-1-ol.

A preferred compound of formula IXa is e.g. 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a prodrug thereof.

S1P receptor agonists or modulators are known as having immunosuppressive properties or anti-angiogenic properties in the treatment of tumors, e.g. as disclosed in EP627406A1, WO 04/103306, WO 05/000833, WO 05/103309, WO 05/113330 or WO 03/097028.

Multiple sclerosis (MS) is an immune-mediated disease of the central nervous system with chronic inflammatory demyelination leading to progressive decline of motor and sensory functions and permanent disability. The therapy of multiple sclerosis is only partially effective, and in most cases only offers a short delay in disease progression despite anti-inflammatory and immunosuppressive treatment. Accordingly,

there is a need for agents which are effective in the inhibition or treatment of demyelinating diseases, e.g. multiple sclerosis or Guillain-Barré syndrome, including reduction of, alleviation of, stabilization of or relief from the symptoms which affect the organism.

Characteristic pathological features of demyelinating diseases include inflammation, demyelination and axonal and oligodendrocyte loss. In addition lesions can also have a significant vascular component. A firm link has recently been established between chronic inflammation and angiogenesis and neovascularization seems to have a significant role in the progression of disease.

It has now been found that S1P receptor modulators have an inhibitory effect on neo-angiogenesis associated with demyelinating diseases, e.g. MS.

In a series of further specific or alternative embodiments, the present invention provides:

1.1. A method for preventing, inhibiting or treating neo-angiogenesis associated with a demyelinating disease, e.g. MS, in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of an S1P receptor modulator, e.g. a compound of formulae I to IXb.

1.2. A method for alleviating or delaying progression of the symptoms of a demyelinating disease, e.g. multiple sclerosis or Guillain-Barré syndrome, in a subject in need thereof, in which method neo-angiogenesis associated with said disease is prevented or inhibited, comprising administering to said subject a therapeutically effective amount of an S1P receptor modulator, e.g. a compound of formulae I to IXb.

1.3. A method for reducing or preventing or alleviating relapses in a demyelinating disease, e.g. multiple sclerosis or Guillain-Barré syndrome, in a subject in need thereof, in which method neo-angiogenesis associated with said disease is prevented or inhibited, comprising administering to said subject a therapeutically effective amount of an S1P receptor modulator, e.g. a compound of formulae I to IXb.

1.4. A method for slowing progression of a demyelinating disease, e.g. multiple sclerosis or Guillain-Barré syndrome, in a subject being in a relapsing-remitting phase of the disease, in which method neo-angiogenesis associated with said disease is prevented or inhibited, comprising administering to said subject a therapeutically effective amount of an S1P receptor modulator, e.g. a compound of formulae I to XIb.

1.5. A method as indicated above, wherein the S1P receptor modulator is administered intermittently.

For example, the S1P receptor modulator may be administered to the subject every 2^{nd} or 3^{rd} day or once a week.

2. A pharmaceutical composition for use in any one of the methods 1.1 to 1.5, comprising an S1P receptor modulator, e.g. a compound of formulae I to IXb as defined hereinabove, together with one or more pharmaceutically acceptable diluents or carriers therefor.

3. An S1P receptor modulator, e.g. a compound of formula I to IXb as defined herein above, for use in any one of the methods 1.1 to 1.5.

4. An S1P receptor modulator, e.g. a compound of formulae I to IXb as defined herein above, for use in the preparation of a medicament for use in any one of the methods 1.1 to 1.5.

Clinicians usually categorize patients having MS into four types of disease patterns:

Relapsing-remitting (RR-MS): Discrete motor, sensory, cerebellar or visual attacks that occur over 1-2 weeks and often resolve over 1-2 months. Some patients accrue disability with each episode, yet remain clinically stable between relapses. About 85% of patients initially experience the RR form of MS, but within 10 years about half will develop the secondary progressive form.

Secondary-progressive (SP-MS): Initially RR followed by gradually increasing disability, with or without relapses. Major irreversible disabilities appear most often during SP.

Primary-progressive (PP-MS): Progression disease course from onset without any relapses or remissions, affecting about 15% of MS patients.

Progressive-relapsing (PR-MS): Progressive disease from onset with clear acute relapses; periods between relapses characterized by continuing progression.

Accordingly, the S1P receptor modulators, e.g. a compound of formulae I to IXb as defined hereinabove, may be useful in the treatment of one or more of Relapsing-remitting (RR-MS), Secondary-progressive (SP-MS), Primary-progressive (PP-MS) and Progressive-relapsing (PR-MS).

In particular, the S1P receptor modulators as described herein, e.g. FTY720, i.e. 2-amino-2-[2-(4-octylphenyl)ethyl] propane-1,3-dio, are useful for treating PP-MS.

Utility of the S1P receptor modulators, e.g. the S1P receptor modulators comprising a group of formula X, in preventing or treating neo-angiogenesis associated with a demyelinating disease as hereinabove specified, may be demonstrated in animal test methods as well as in clinic, for example in accordance with the methods hereinafter described.

In Vivo: Relapsing Experimental Autoimmune Encephalomyelitis (EAE)

Disease is induced in female Lewis rats by immunization with guinea pig spinal cord tissue emulsified in complete Freund's adjuvant. This results in an acute disease within 11 days, followed by an almost complete remission around day 16 and a relapse at around days 26.

On day 26 rats are thoracectomized after having been deeply anesthetized with Isoflurane (3%, 20 L/min) and perfused through the left ventricle of the heart. The left ventricle is punctured with a 19 gauge needle from a winged infusion set (SV-19BLK; Termudo, Elkton, Md.), which is connected to an airtight pressurized syringe containing the rinsing solution (NaCl 0.9% with 250,000 U/l heparin at 35° C.). The right atrium is punctured to provide outflow, and the perfusate is infused under a precise controlled pressure of 120 mm Hg. The perfusion is continued for 5 min (at a constant rate of 20 ml/min) followed by a pre-fixation solution (2% performaldehyde in PBS at 35° C.). Finally, up to 30 ml of polyurethane resin (PUI14; Vasqtec, Zürich, Switzerland) is infused at the same rate. After 48 h, the resin-filled brain and spinal cord are excised from the animal and the soft tissue removed by maceration in 7.5% KOH during 24 hr at 50° C. The casts are then thoroughly cleaned with and stored in distilled water before drying by lyophilization. These vascular casts are quantitated using micro computer tomography.

In this assay, a S1P1 receptor modulator, e.g. Compound A significantly blocks disease-associated neo-angiogenesis when administered to the animals at a dose of from 0.1 to 20 mg/kg p.o. For example, Compound A, in the hydrochloride salt form, fully blocks disease-associated angiogenesis and completely inhibits the relapse phases when administered daily at a dose of 0.3 mg/kg p.o. The same effect is obtained

when Compound A, in the hydrochloride salt form, is administered p.o. at 0.3 mg/kg every 2nd or 3rd day or once a week.

C. Clinical Trial

Investigation of clinical benefit of a S1P receptor agonist, e.g. a compound of formula I, e.g. Compound A.

20 patients with relapsing-remitting MS receive said compound at a daily dosage of 0.5, 1.25 or 2.5 mg p.o. The general clinical state of the patient is investigated weekly by physical and laboratory examination. Disease state and changes in disease progression are assessed every 2 months by radiological examination (MRI) and physical examination. Initially patients receive treatment for 2 to 6 months. Thereafter, they remain on treatment for as long as their disease does not progress and the drug is satisfactorily tolerated.

Main variables for evaluation: Safety (adverse events), standard serum biochemistry and hematology, magnetic resonance imaging (MRI).

Daily dosages required in practicing the method of the present invention when a S1P receptor modulator alone is used will vary depending upon, for example, the compound used, the host, the mode of administration and the severity of the condition to be treated. A preferred daily dosage range is about from 0.1 to 100 mg as a single dose or in divided doses. Suitable daily dosages for patients are on the order of from e.g. 0.1 to 50 mg p.o. The S1P receptor modulator may be administered by any conventional route, in particular enterally, e.g. orally, e.g. in the form of tablets, capsules, drink solutions, nasally, pulmonary (by inhalation) or parenterally, e.g. in the form of injectable solutions or suspensions. Suitable unit dosage forms for oral administration comprise from ca. 0.1 to 30 mg, usually 0.25 to 30 mg S1P receptor modulator, together with one or more pharmaceutically acceptable diluents or carriers therefore. As already mentioned, the S1P receptor modulator, e.g. Compound A, may alternatively be administered intermittently, e.g. at a dose of 0.5 to 30 mg every other day or once a week.

According to another embodiment of the invention, the S1P receptor modulator may be administered as the sole active ingredient or in conjunction with, e.g. as an adjuvant to, a VEGF-receptor antagonist.

Examples of suitable VEGF-receptor antagonist include e.g. compounds, proteins or antibodies which inhibit the VEGF receptor tyrosine kinase, inhibit a VEGF receptor or bind to VEGF, and are e.g. in particular those compounds, proteins or monoclonal antibodies generically and specifically disclosed in WO 98/35958, e.g. 1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine or a pharmaceutically acceptable salt thereof, e.g. the succinate, in WO 00/27820, e.g. a N-aryl(thio) anthranilic acid amide derivative e.g. 2-[(4-pyridyl)methyl]amino-N-[3-methoxy-5-(trifluoromethyl)phenyl]benzamide or 2-[(1-oxido-4-pyridyl)methyl]amino-N-[3-trifluoromethylphenyl]benzamide, or in WO 00/09495, WO 00/59509, WO 98/11223, WO 00/27819, WO 01/55114, WO 01/58899 and EP 0 769 947; those as described by M. Prewett et al in Cancer Research 59 (1999) 5209-5218, by F. Yuan et al in Proc. Natl. Acad. Sci. USA, vol. 93, pp. 14765-14770, December 1996, by Z. Zhu et al in Cancer Res. 58, 1998, 3209-3214, and by J. Mordenti et al in Toxicologic Pathology, Vol. 27, no. 1, pp 14-21, 1999; in WO 00/37502 and WO 94/10202; Angiostatin™, described by M. S. O'Reilly et al, Cell 79, 1994, 315-328; Endostatin™, described by M. S. O'Reilly et al, Cell 88, 1997, 277-285; anthranilic acid amides; ZD4190; ZD6474; SU5416; SU6668; or anti-VEGF antibodies or anti-VEGF receptor antibodies, e.g. RhuMab.

4-Pyridylmethyl-phthalazine derivatives are e.g. preferred inhibitors of VEGF receptor tyrosine kinase. Such derivatives and their preparation, pharmaceutical formulations thereof and methods of making such compounds are described in WO00/59509, EP02/04892, WO01/10859 and, in particular, in U.S. Pat. No. 6,258,812, which are here incorporated by reference.

Where the S1P receptor modulator is administered in conjunction with a VEGF-receptor antagonist, dosages of the co-administered VEGF-receptor agonist will of course vary depending on the type of co-drug employed, e.g. whether it is a steroid or a calcineurin inhibitor, on the specific drug employed, on the condition being treated and so forth. In accordance with the foregoing the present invention provides in a yet further aspect:

5. A method as defined above comprising co-administration, e.g. concomitantly or in sequence, of a therapeutically effective non-toxic amount of a S1P receptor modulator and a VEGF-receptor antagonist, e.g. as indicated above.
6. A pharmaceutical combination, e.g. a kit, comprising a) a first agent which is a S1P receptor modulator as disclosed herein, in free form or in pharmaceutically acceptable salt form, and b) a VEGF-receptor antagonist, e.g. as indicated above. The kit may comprise instructions for its administration.

The terms "co-administration" or "combined administration" or the like as utilized herein are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time.

The term "pharmaceutical combination" as used herein means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that the active ingredients, e.g. a S1P receptor modulator and a VEGF-receptor antagonist, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that the active ingredients, e.g. a S1P receptor modulator and a VEGF-receptor antagonist, are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the 2 compounds in the body of the patient.

The invention claimed is:

1. A method for reducing or preventing or alleviating relapses in Relapsing-Remitting multiple sclerosis in a subject in need thereof, comprising orally administering to said subject 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol, in free form or in a pharmaceutically acceptable salt form, at a daily dosage of 0.5 mg, absent an immediately preceding loading dose regimen.

2. The method according to claim **1** wherein 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride is administered.

3. A method for treating Relapsing-Remitting multiple sclerosis in a subject in need thereof, comprising orally administering to said subject 2-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol, in free form or in a pharmaceutically acceptable salt form, at a daily dosage of 0.5 mg, absent an immediately preceding loading dose regimen.

4. The method according to claim **3** wherein 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride is administered.

5. A method for slowing progression of Relapsing-Remitting multiple sclerosis in a subject in need thereof, comprising orally administering to said subject 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol, in free form or in a pharmaceutically acceptable salt form, at a daily dosage of 0.5 mg, absent an immediately preceding loading dose regimen.

6. The method according to claim 5 wherein 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride is administered.

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FORM 19. Certificate of Compliance with Type-Volume Limitations **Form 19**
July 2020

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATIONS

Case Number: 2021-1070

Short Case Caption: Novartis Pharmaceuticals v. Accord Healthcare Inc.

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