APPENDICES

Appendix A

United States Court of Appeals for the Federal Circuit

NOVARTIS PHARMACEUTICALS CORPORATION,
Plaintiff-Appellee

v.

ACCORD HEALTHCARE, INC., AUROBINDO PHARMA LTD., AUROBINDO PHARMA USA, INC., DR. REDDY'S LABORATORIES, INC., DR. REDDY'S LABORATORIES, LTD., EMCURE PHARMACEUTICALS LTD., 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 LIMITED, STRIDES PHARMA, INC., TORRENT PHARMA INC., TORRENT PHARMACEUTICALS LTD., ZYDUS PHARMACEUTICALS (USA) INC., CADILA HEALTHCARE LTD., 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

2021-1070

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

Decided: June 21, 2022

JANE M. LOVE, Gibson, Dunn & Crutcher LLP, New York, NY, argued for plaintiff-appellee. Also represented by PAUL E. TORCHIA, ROBERT TRENCHARD.

PAUL SKIERMONT, Skiermont Derby LLP, Dallas, TX, argued for defendants-appellants. Also represented by SARAH ELIZABETH SPIRES; MIEKE K. MALMBERG, Los Angeles, CA.

Before MOORE, *Chief Judge*, LINN and HUGHES, *Circuit Judges*.

Opinion for the court filed by *Chief Judge* MOORE.

Dissenting opinion filed by *Circuit Judge* LINN.

MOORE, *Chief Judge*.

HEC Pharm Co., Ltd. and HEC Pharm USA Inc. (collectively, HEC) petition for rehearing of our prior decision in this case, 21 F.4th 1362 (Fed. Cir. 2022), in which we affirmed a final judgment of the United States District Court for the District of Delaware. The district court determined that claims 1–6 of U.S. Patent No. 9,187,405 are not invalid and that HEC infringes them. Because the '405 patent fails to disclose the absence of a loading dose, the district court clearly erred in finding that the negative claim limitation "absent an immediately preceding loading dose" added during prosecution to overcome prior art

satisfies the written description requirement of 35 U.S.C. § 112(a). We grant HEC's petition for panel rehearing, vacate our prior decision, and reverse the district court's judgment that Novartis' claims are not invalid for inadequate written description.

BACKGROUND

The '405 patent discloses methods of treating relapsing-remitting multiple sclerosis (RRMS) using the immunosuppressant fingolimod. *E.g.*, '405 patent at claim 1, 8:56–60. Each claim of the '405 patent requires administering fingolimod "at a daily dosage of 0.5 mg, absent an immediately preceding loading dose regimen." *Id.* at claim 1. A loading dose is a "higher-than-daily dose . . . usually given as the first dose." J.A. 27 ¶ 63 (internal quotation marks omitted). The patent's specification does not mention loading doses, much less the absence of a loading dose. Instead, it describes administering fingolimod at regular intervals (e.g., once daily, multiple times per day, or every other day). '405 patent at 11:20–38.

Novartis owns the '405 patent and markets a drug under the brand name Gilenya that purportedly practices the patent. HEC filed an abbreviated new drug application (ANDA) with the Food and Drug Administration seeking approval to market a generic version of Gilenya. Novartis sued HEC in the District of Delaware, alleging that HEC's ANDA infringes all claims of the '405 patent.[1]

After a four-day bench trial, the district court found that HEC's ANDA infringes and that the claims are not invalid, either as anticipated by Kappos 2006 or for inadequate written description of the no-loading-dose or daily-

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[1] Novartis sued several other defendants who also filed ANDAs, but those cases were settled or stayed before trial.

dosage limitations. HEC appeals as to written description. We have jurisdiction under 28 U.S.C. § 1295(a)(1).

DISCUSSION

"Whether a claim satisfies the written description requirement is a question of fact that, on appeal from a bench trial, we review for clear error." *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1308 (Fed. Cir. 2015) (quoting *Alcon Rsch. Ltd. v. Barr Labs., Inc.*, 745 F.3d 1180, 1190 (Fed. Cir. 2014)). Under the clear error standard, we defer to the district court's findings "in the absence of a definite and firm conviction that a mistake has been made." *Scanner Techs. Corp. v. ICOS Vision Sys. Corp. N.V.*, 528 F.3d 1365, 1374 (Fed. Cir. 2008) (cleaned up). Inadequate written description must be shown by clear and convincing evidence. *Hynix Semiconductor Inc. v. Rambus Inc.*, 645 F.3d 1336, 1351 (Fed. Cir. 2011) (citing *ICU Med., Inc. v. Alaris Med. Sys., Inc.*, 558 F.3d 1368, 1376 (Fed. Cir. 2009)).

A

To satisfy the written description requirement, a patent's specification must "reasonably convey[ ] to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). Such possession must be "shown in the disclosure." *Id.* It is not enough that a claimed invention is "an obvious variant of that which is disclosed in the specification." *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997). Disclosure is essential; it is "the *quid pro quo* of the right to exclude." *Kewanee Oil Co. v. Bicron Corp.*, 416 U.S. 470, 484 (1974); *see also Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 970 (Fed. Cir. 2002) ("[D]escription is the *quid pro quo* of the patent system.").

For negative claim limitations, like the no-loading-dose limitation at issue here, there is adequate written

description when, for example, "the specification describes a reason to exclude the relevant [element]." *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1351 (Fed. Cir. 2012); *Inphi Corp. v. Netlist, Inc.*, 805 F.3d 1350, 1355 (Fed. Cir. 2015) (same); *Nike, Inc. v. Adidas AG*, 812 F.3d 1326, 1348 (Fed. Cir. 2016) (same), *overruled on other grounds by Aqua Prods., Inc. v. Matal*, 872 F.3d 1290, 1301 (Fed. Cir. 2017) (en banc). A reason to exclude an element could be found in "statements in the specification expressly listing the disadvantages of using" that element. *Santarus*, 694 F.3d at 1351. Another reason could be that the specification "distinguishes among" the element and alternatives to it. *Inphi*, 805 F.3d at 1357; *see also In re Johnson*, 558 F.2d 1008, 1017–19 (C.C.P.A. 1977) (reversing rejection for inadequate written description where specification disclosed several species of a genus and claims recited genus but excluded two species of lost interference count).

The common denominator of these examples is disclosure of the element. That makes sense because "the hallmark of written description is disclosure." *Ariad*, 598 F.3d at 1351; *see also Lockwood*, 107 F.3d at 1571 ("It is the disclosures of the applications that count."). Silence is generally not disclosure. *See Seabed Geosolutions (US) Inc. v. Magseis FF LLC*, 8 F.4th 1285, 1288 (Fed. Cir. 2021) ("[S]ilence does not support reading the claims to exclude gimbaled geophones." (citations omitted)); MPEP § 2173.05(i) (9th ed. Rev. 10.2019, June 2020) ("The mere absence of a positive recitation is not a basis for an exclusion."). If it were, then every later-added negative limitation would be supported so long as the patent makes no mention of it. While a negative limitation need not be recited in the specification *in haec verba*, there generally must be something in the specification that conveys to a skilled artisan that the inventor intended the exclusion, such as a discussion of disadvantages or alternatives. Consistent with our precedent in *Santarus*, *Inphi* and *Nike*, the

written description requirement cannot be met through simple disregard of the presence or absence of a limitation.

While a written description's silence about a negative claim limitation is a useful and important clue and may often be dispositive, it is possible that the written description requirement may be satisfied when a skilled artisan would understand the specification as inherently disclosing the negative limitation.[2] For example, if the record established that in a particular field, the absence of mention of a limitation necessarily excluded that limitation, written description could be satisfied despite the specification's silence. *See Tronzo v. Biomet, Inc.*, 156 F.3d 1154, 1159 (Fed. Cir. 1998) ("[M]issing descriptive matter must necessarily be present in the . . . specification such that one skilled in the art would recognize such a disclosure." (citing *Cont'l Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991))); *see also In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999) ("To establish inherency [for purposes of anticipation], . . . evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." (internal quotation

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[2] Novartis contends the written description requirement may be satisfied by "implicit disclosure" as distinct from express or inherent disclosure. Novartis Br. 50–51. Yet it fails to identify any case holding that "implicit disclosure" (whatever that means) is sufficient. Novartis cites *In re Kolstad*, a non-precedential decision involving *express* disclosure. 907 F.2d 157 (Fed. Cir. 1990) (non-precedential). If an implicit disclosure is one that would render the limitation obvious to a skilled artisan, such a disclosure cannot under our precedent satisfy the written description requirement. *Lockwood*, 107 F.3d at 1572 ("A description which renders obvious the invention for which an earlier filing date is sought is not sufficient.").

marks and citation omitted)). When the specification is itself silent regarding a negative limitation, testimony from a skilled artisan as to possibilities or probabilities that the recited element would be excluded would not suffice, lest such testimony could effectively eliminate the written description requirement. If silence were generally sufficient, all negative limitations would be supported by a silent specification. If, however, a patent owner could establish that a particular limitation would always be understood by skilled artisans as being necessarily excluded from a particular claimed method or apparatus if that limitation is not mentioned, the written description requirement would be satisfied despite the specification's silence.

B

The district court found that because there is no recitation of a loading dose in the specification, the no-loading-dose limitation is supported. J.A. 26 ¶ 61. The district court further found that the no-loading-dose limitation is disclosed in the specification because "[t]he Prophetic Trial describes giving a 'daily dosage of 0.5 . . . mg' fingolimod to treat RRMS, started 'initially.' 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." J.A. 26 ¶ 62 (citations omitted). Novartis, likewise, argues that the specification satisfies the written description requirement for the no-loading-dose limitation because it indicates that the dosing regimen starts by "initially" administering a daily dosage. Novartis Br. 44.

The district court's finding that the specification discloses "initially" starting with a daily dose was clearly erroneous. The specification nowhere describes "initially" administering a daily dosage. The specification says, "Initially patients receive treatment for 2 to 6 months." '405 patent at 11:13–14. This sentence speaks to the initial length of treatment, not the dosage with which treatment

begins. Dr. Lublin, one of Novartis' physician experts, admitted this:

> Q. And then . . . there's a sentence that begins: Initially, patients receive treatment for two to six months. Do you see that?
>
> A. I do.
>
> Q. And what does that tell you about how the dosing would work?
>
> A. It suggests to me they're taking the dosing that's outlined in that first sentence *continually for two to six months*.

J.A. 22792 (emphasis added).

The contrary testimony of Novartis' second physician expert, Dr. Steinman, is inconsistent with the plain text of the specification and therefore carries no weight. J.A. 23343 (testifying that "initially" is "really zooming in on Day 1" and conveying that treatment starts with "a daily dose of 0.5"). "[E]xpert testimony that is inconsistent with unambiguous intrinsic evidence should be accorded no weight." *Bell & Howell Document Mgmt. Prods. Co. v. Altek Sys.*, 132 F.3d 701, 706 (Fed. Cir. 1997) (citations omitted). As HEC argues in its rehearing petition, the district court's reliance on a misquotation "ferreted into trial testimony by Novartis' experts" was clearly erroneous. Pet. for Reh'g 6; *see* J.A. 26–27 ¶¶ 62–63 (district court relying on testimony that specification describes "initially" administering daily dosage).

The '405 specification discloses neither the presence nor absence of a loading dose. Loading doses—whether to be used or not—are simply not discussed. Novartis' experts readily admitted this. J.A. 23344 ("Q. Is there anywhere in [the specification] that you saw reference to the loading dose? A. No."); J.A. 22791 (Dr. Lublin testifying that "information of having a loading dose is not there"). Dr.

Lublin also agreed that "[n]othing in the text of the specification of the '405 patent discloses a rationale for the negative limitation prohibiting an immediately preceding loading dose." J.A. 22872–73. The fact that the specification is silent about loading doses does not support a later-added claim limitation that precludes loading doses.

The district court also found, independent of the misquoted "initially" language, that the specification's disclosure of a daily dosage combined with its silence regarding a loading dose would "tell a person of skill that loading doses are excluded from the invention." J.A. 26 ¶ 61. That, too, was clearly erroneous. Novartis does not defend this finding.[3] And for good reason.

There is significant tension in the district court's finding that the specification's disclosure excludes a loading dose, but that the Kappos 2006 abstract does not. Both are silent regarding loadings doses, and both disclose a daily dosage. The district court defended this inconsistency by claiming that "[u]nlike a patent, which is presumed complete, an abstract [like Kappos 2006] is not presumed to contain all of the necessary information about the study." J.A. 30 ¶ 74. This concept that a patent is presumed "complete" infected the district court's analysis and the experts' testimony regarding the no-loading-dose limitation. For example, Dr Lublin testified:

> Q. What would a person of skill reading the patent have thought about [the] question [of written description]?
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> A. They would have viewed the patent as a document, as a complete document, that should give you

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[3] Nor could it. Novartis admittedly did not "argue below that inherency . . . applies to the '405 Patent's method claims." Novartis Br. 50. Any defense of the district court's finding is thus forfeit.

> all the information you need to carry out the claims, and that information of having a loading dose is not there, and what's instead there is examples of daily dose, daily dose, daily dose.

J.A. 22791. A patent is not presumed complete such that things not mentioned are necessarily excluded. We presume only that a patent has adequate written description, not that it is complete. *Nat'l Recovery Techs., Inc. v. Magnetic Separation Sys., Inc.*, 166 F.3d 1190, 1195 (Fed. Cir. 1999) ("The presumption of validity includes a presumption that the patent complies with § 112." (citing *N. Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 941 (Fed. Cir. 1990))).

Importantly, the disclosure of a daily dosage cannot amount to a disclosure that there can be no loading dose, because such a finding is at odds with the prosecution history. The Patent Office allowed the claims only after the applicants added the no-loading-dose limitation. J.A. 23903 (examiner's rejection in parent application); J.A. 23892–93 (applicants' response); *see also* Novartis Br. 11–12. The applicants explained that they added the no-loading-dose limitation "to specify that the [daily dosage] cannot immediately follow a loading dose regimen" and "to further distinguish their claims from the disclosure of [prior art]." J.A. 23892. If reciting "daily dosage" without mentioning a loading dose necessarily excluded a loading dose, there would have been no reason for the applicants to add the no-loading-dose limitation. Neither the applicants nor the examiner understood the words "daily dosage" without the words "no loading dose" to convey the absence of a loading dose. Accordingly, the district court's contrary finding was clearly erroneous.

There is expert testimony that the specification discloses the absence of a loading dose. Dr. Steinman testified:

> Q. And do you see the sentence there, it says, "Initially patients receive treatment for 2 to 6 months." What would that tell a person of skill?
>
> A. Well, there were two places [in the specification] that if there were going to be an immediately preceding loading dose, you would give it before the initial treatment, so you would really necessarily want to put it right there. And the second place was earlier when you talked about a daily dosage of 0.5. But there were two gates that if you wanted to interject something about a loading dose, those were the opportunities in this. And it was zero out of two places where they, I think, necessarily would have put it in.

J.A. 23334–35. This expert testimony is focused on where in the specification the patentee would have mentioned a loading dose if they intended a loading dose to be included. But the question is not whether the patentee intended there to be a loading dose; the question is whether the patentee precluded the use of a loading dose. On this record, there is no evidence that a skilled artisan would understand silence regarding a loading dose to *necessarily exclude* a loading dose. In fact, all the experts agreed that loading doses are sometimes given to MS patients. *See* J.A. 22780 (Dr. Lublin explaining that loading doses have been used in trials of MS drugs and with fingolimod in particular); J.A. 22794; J.A. 23347–48 (Dr. Steinman acknowledging that loading doses are used in MS treatments); J.A. 23475 (Dr. Jusko, Novartis' pharmacology expert, testifying that fingolimod was given to transplant patients with a loading dose, and that he "could envision the possibility of starting with a loading dose"). And, importantly, there is intrinsic evidence that a skilled artisan would not understand reciting a daily dosage regimen without mentioning a loading dose to exclude a loading dose.

We do not today create a heightened standard for negative claim limitations. Just as disclosure is the "hallmark of written description" for positive limitations, *Ariad*, 598 F.3d at 1351, so too for negative limitations. That disclosure "need not rise to the level of disclaimer." *Santarus*, 694 F.3d at 1351. Nor must it use the same words as the claims. *Lockwood*, 107 F.3d at 1572 ("[T]he exact terms need not be used *in haec verba*." (citing *Eiselstein v. Frank*, 52 F.3d 1035, 1038 (Fed. Cir. 1995))). Rather, as with positive limitations, the disclosure must only "reasonably convey[ ] 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. While silence will not generally suffice to support a negative claim limitation, there may be circumstances in which it can be established that a skilled artisan would understand a negative limitation to necessarily be present in a disclosure. This is not such a case.

CONCLUSION

The district court's finding that the no-loading-dose limitation meets the written description requirement was clearly erroneous. We grant HEC's petition for panel rehearing, vacate our prior decision, and reverse the district court's judgment that the claims of the '405 patent are not invalid. We need not reach HEC's argument that the district court also clearly erred in finding adequate written description for the "daily dosage of 0.5 mg" limitation.

REVERSED

COSTS

No costs.

United States Court of Appeals for the Federal Circuit

NOVARTIS PHARMACEUTICALS CORPORATION,
Plaintiff-Appellee

v.

ACCORD HEALTHCARE, INC., AUROBINDO PHARMA LTD., AUROBINDO PHARMA USA, INC., DR. REDDY'S LABORATORIES, INC., DR. REDDY'S LABORATORIES, LTD., EMCURE PHARMACEUTICALS LTD., 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 LIMITED, STRIDES PHARMA, INC., TORRENT PHARMA INC., TORRENT PHARMACEUTICALS LTD., ZYDUS PHARMACEUTICALS (USA) INC., CADILA HEALTHCARE LTD., 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.,
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2021-1070

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

LINN, *Circuit Judge*, dissenting.

The majority, while recognizing that written description support is a fact-based inquiry based on the understandings of a person of ordinary skill in the art, and while ultimately recognizing that the standard for negative limitations is the same as for any other limitation, nonetheless applies a heightened written description standard to the facts of this case in requiring not only a "reason to exclude" but a showing that the negative limitation in question was "necessarily excluded." In doing so, the majority characterizes the district court's fact finding as clearly erroneous and concludes that written description support for the no-load limitation is lacking. In my opinion, the district court applied the correct standard and found ample support in the written description for the no-load limitation. For these reasons, I respectfully dissent.

I

A specification that "reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date" has adequate written description of the claimed invention. *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010). "[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.* Our case law makes clear that "[c]ompliance with the written description requirement is essentially a fact-based inquiry that will 'necessarily vary depending on the nature of the invention claimed.'" *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 963 (Fed. Cir. 2002) (quoting *Vas-Cath Inc. v.*

Mahurkar, 935 F.2d 1555, 1562 (Fed. Cir. 1991)). It is well established that there is no "new and heightened standard for negative claim limitations." *Inphi Corp. v. Netlist, Inc.*, 805 F.3d 1350, 1356 (Fed. Cir. 2015). While the court in *Santarus, Inc. v. Par Pharmaceutical, Inc.* observed that "[n]egative claim limitations are adequately supported when the specification describes a reason to exclude the relevant limitation," we did not hold that a specification *must* describe a reason to exclude a negative limitation. 694 F.3d 1344, 1351 (Fed. Cir. 2012). A specification that describes a reason to exclude the relevant negative limitation is but one way in which the written description requirement may be met.

The majority begins its opinion with the recognition that a written description's silence about a negative claim limitation, while serving as a "useful and important clue," is not necessarily dispositive of whether that limitation is adequately supported. Maj. at 6. I agree. The majority concludes with a citation to *Ariad* for the proposition that "as with positive limitations, the disclosure must only 'reasonably convey [] to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date.'" Maj. at 12 (citing *Ariad*, 598 F.3d at 1351). With that, I also agree. But the majority in its analysis employs the heightened standard of "necessary exclusion" against which to assess the district court's fact findings in this case and uses that standard to conclude that the district court clearly erred. With that, I cannot agree. While a showing of "necessary exclusion" would most certainly provide written description support for a negative limitation, it is not and should not be a requirement in every case. As noted above and as *Ariad* makes clear, the critical question in assessing written description support for a negative limitation is the same as for any other limitation: "Does the written description reasonably convey to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date?" *See Ariad*, 598 F.3d

at 1351. How that question is resolved depends on the facts of each case, assessed through the eyes of the skilled artisan. Our precedent makes that clear.

For example, in *Santarus*, we found that claims directed to a method of treatment with a pharmaceutical composition containing no sucralfate were adequately described by a specification that explained that, although sucralfate is "possibly the ideal agent for stress ulcer prophylaxis," it was known to have occasional adverse effects. 694 F.3d 1344, 1350–51 (Fed. Cir. 2012). In *Santarus*, as in this case, there was expert testimony providing a person of ordinary skill's understanding of the patent specification. *See id.* at 1351. The expert testimony in *Santarus* showed that "a person of ordinary skill in this field . . . would have understood from the specification that disadvantages of sucralfate may be avoided by the [claimed] formulation." *Id.*

In *In re Bimeda Research & Development Ltd.*, we held that a claim that excluded a specific anti-infective, acriflavine, was not adequately described by a disclosure that was inconsistent with the exclusion of acriflavine but not other anti-infectives or antibiotics. 724 F.3d 1320, 1324 (Fed. Cir. 2013). The claim at issue in *Bimeda* was directed to a method of preventing mastitis in dairy cows by sealing the teat canal of a cow's mammary gland with a seal formulation that excludes acriflavine. Other claims in the same patent excluded all anti-infective agents. We noted that the patent repeatedly distinguished the invention as able to prevent mastitis without the use of antibiotics. Based on the written description's consistent description of the invention's non-antibiotic approach to preventing mastitis, we concluded that the patent's disclosure was "inconsistent with a claim which excludes acriflavine, but *not* the presence of other anti-infectives or antibiotics." *Id.* (citation and quotation marks omitted). We did not require that the specification describe a reason to exclude acriflavine specifically; rather, we found only that a negative limitation

which is inconsistent with the disclosure is not adequately described.

In *Inphi*, we confirmed that the written description requirement is satisfied where "'the essence of the original disclosure' conveys the necessary information—'regardless of *how* it' conveys such information, and regardless of whether the disclosure's 'words [a]re open to different interpretation[s].'" 805 F.3d at 1354 (quoting *In re Wright*, 866 F.2d 422, 424–25 (Fed. Cir. 1989) (citation and internal quotation marks omitted, emphasis in *Inphi*)). We explained that "*Santarus* simply reflects the fact that the specification need only satisfy the requirements of § 112, paragraph 1 as described in this court's existing jurisprudence." *Id.* at 1356. And we noted that the "'reason' required by *Santarus* is provided, for instance, by properly describing alternative features of the patented invention." *Id.* (citing *In re Johnson*, 558 F.2d 1008, 1019 (C.C.P.A. 1977)).

In *Inphi*, we found that substantial evidence supported the Patent Trial and Appeal Board's ("Board") finding that a negative limitation which had been added during prosecution ("DDR chip selects that are not CAS, RAS, or bank address signals") was adequately described by an original specification which did not expressly articulate a reason to exclude RAS and CAS signals. We found the Board's decision was supported by evidence of (1) standards set by the Joint Electron Device Engineering Council, a global standard-setting body for the microelectronics industry, incorporated by reference in the patent, which specify that DDR signals, including CAS, RAS, CAS, and bank address signals, are distinct from each other; (2) a table in the specification which excludes RAS and CAS signals; and (3) various passages from the specification, including a figure which distinguishes chip select signals, command signals (including RAS and CAS signals) and bank address signals. We concluded that the specification's disclosure of

alternative features was sufficient to satisfy the written description standard for the negative limitation. *Id.* at 1357.

In *Nike, Inc. v. Adidas AG*, we reiterated that *Santarus* did not create a heightened standard for written description of negative limitations. 812 F.3d 1326, 1348 (Fed. Cir. 2016), *overruled on other grounds by Aqua Prods., Inc. v. Matal*, 872 F.3d 1290 (Fed. Cir. 2017) (en banc). We stated that negative limitations, like all other limitations, are held to "the customary standard for the written description requirement." *Id.* In *Nike*, we found a limitation of "flat knit edges," which Adidas characterized as a negative limitation, was adequately described by three figures in the specification depicting the claimed textile element which Nike's expert opined could be made using flat knitting in contrast to another figure's textile element which is formed using a circular knitting machine. *Id.* at 1348–49.

The central tenet of our written description jurisprudence—that the disclosure must be read from the perspective of a person of skill in the art—further recognizes that the disclosure need not describe a limitation *in haec verba*. *See, e.g.*, *All Dental Prods., LLC v. Advantage Dental Prod., Inc.*, 309 F.3d 774, 779 (Fed. Cir. 2002) (citing *Eiselstein v. Frank*, 52 F.3d 1035, 1039 (Fed. Cir. 1995) ("[T]he failure of the specification to specifically mention a limitation that later appears in the claims is not a fatal one when one skilled in the art would recognize upon reading the specification that the new language reflects what the specification shows has been invented."); *see also Ariad*, 598 F.3d at 1351.

The Manual of Patent Examining Procedure ("MPEP") similarly provides for written description in various forms. In addition to stating that the "mere absence of a positive recitation" is not enough, the MPEP also correctly states that no specific form of disclosure is required and provides

for implicit written description.[1] MPEP § 2173.05(i) states that "a lack of literal basis in the specification for a negative limitation may not be sufficient to establish a *prima facie* case for lack of descriptive support." And MPEP § 2163 states that "newly added claims or claim limitations must be supported in the specification through express, *implicit*, or inherent disclosure." MPEP § 2163 (emphasis added). What is critical is how a person of skill in the art would read the disclosure—not the exact words used.

In other words, context and the knowledge of those skilled in the art matter. And, as the Supreme Court has made clear, when assessing what the written description reveals to a skilled artisan, common sense also matters. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007) (holding that, in an obviousness analysis, "[r]igid preventative rules that deny factfinders recourse to common sense, however, are neither necessary under our case law nor consistent with it").

II

Here, the district court conducted "an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art" and found sufficient written description in the EAE model and the Prophetic Trial. J.A. 37 (citing *Ariad*, 598 F.3d at 1351). The district court found that the "Prophetic Trial describes giving a 'daily dosage of 0.5 . . . mg' fingolimod to treat RRMS, started 'initially.'" J.A. 26 ¶ 62 (quoting '405 patent col. 11 ll. 8–13). The court found, crediting expert testimony, that, "[i]f a loading dose were directed, the Patent would say that a loading dose should be administered 'initially.'" J.A. 26 ¶ 62 (citing J.A. 23334–35 (Tr.

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[1] I cite the MPEP, not because the court is bound by it but because I find its reasoning informative and persuasive.

756:16–757:8); J.A. 23441–42 (Tr. 863:22–864:18)). The district court thus made the unremarkable, and factually supported, determination that "starting with a daily dose plainly implies that there is no loading dose." J.A. 27. Similarly, the district court found that the "EAE example discloses a dosing regimen which does not involve a loading dose." J.A. 27 ¶ 64 (citing J.A. 23345 (Tr. 767:3–5); J.A. 22793 (Tr. 215:16–21)). The district court held that the description in the specification of administration of a daily dose "would tell a person of skill that loading doses are excluded from the invention." J.A. 26 ¶ 61. The court also found that "[a] loading dose is necessarily a higher-than daily dose." J.A. 27 ¶ 63 (Tr. 766:4-766:6). Finally, the court found that, while the patent describes alternate dosing regimens, such as "intermittent dosing," it does not describe administering those regimens with loading doses. J.A. 27 ¶ 65. Thus, the district court concluded, "[t]he EAE model and the Prophetic Trial . . . indicate to a person of ordinary skill that the claimed invention did not include the administration of a loading dose." J.A. 37–38. The cited passages of the specification provide clear disclosure of a dosing regimen that is not dependent upon or subject to the administration of a loading dose.

The majority finds that the word "initially" "speaks to the initial length of treatment not the dosage with which treatment begins." Maj. at 7–8. Here, the district court found that the "Prophetic Trial describes giving a 'daily dosage of 0.5 . . . mg' fingolimod to treat RRMS, started 'initially.'" J.A. 26. While other interpretations of the word "initially" might be reasonable, the language, used in context, also supports the district court's finding that the written description discloses excluding a loading dose. We are not free to substitute our own factual findings for those of the district court absent clear error because "a district court judge who has presided over, and listened to, the entire proceeding has a comparatively greater opportunity to gain the necessary 'familiarity with specific scientific problems and principles,' . . . than an

appeals court judge who must read a written transcript or perhaps just those portions referenced by the parties." *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 574 U.S. 318, 319 (2015) (quoting *Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, 339 U.S. 605, 610 (1950)).

The majority asserts that the disclosure of a daily dosage cannot amount to a disclosure that there can be no loading dose, because such a finding is at odds with the prosecution history and the fact that the examiner allowed the claims only after the no-load limitation was added. Maj. at 10. According to the majority, if reciting a "daily dosage" necessarily excluded a loading dose, there would have been no reason to add the no-dose limitation. *Id.* at 10:19-22. But Novartis, in adding the no-load limitation was doing no more than what applicants regularly do to secure allowance in making explicit that which was implicit prior to the amendment. There is no basis to read more into the prosecution history and certainly no basis to negate the clear disclosure of a "daily dosage" and the expert testimony describing the understanding of that expression to skilled artisans.

The majority asserts that "the question is not whether the patentee intended there to be a loading dose; the question is whether the patentee precluded the use of a loading dose." Maj. at 11. I submit that the question posed by the majority is misstated. The question is not whether the patentee precluded the use of a loading dose but whether the claim language that precludes the administration of a loading dose is supported by the written description passages that disclose the effective administration of nothing more than a "daily dose." In context, that disclosure, according to the testimony of the Novartis's experts, implies the absence of a loading dose to the ordinarily skilled artisan. That is all that is required.

Finally, the majority finds significant tension between the district court's finding that the specification's

disclosure excludes a loading dose, but the Kappos 2006 abstract does not. Maj. at 9. I see no tension or legal inconsistency in the district court's treatment of the Kappos 2006 abstract. As the court explained, Kappos was an abstract with no presumption of enablement or completeness, and it in any event did not include the animal trials that form an important part of Novartis's arguments with respect to the '405 patent. As importantly, the district court also found no evidence that Kappos 2006 was publicly available before the priority date because there was no evidence of public access. J.A. 28.

For all these reasons, I respectfully dissent.

Appendix B

United States Court of Appeals for the Federal Circuit

NOVARTIS PHARMACEUTICALS CORPORATION,
Plaintiff-Appellee

v.

ACCORD HEALTHCARE, INC., AUROBINDO PHARMA LTD., AUROBINDO PHARMA USA, INC., DR. REDDY'S LABORATORIES, INC., DR. REDDY'S LABORATORIES, LTD., EMCURE PHARMACEUTICALS LTD., 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 LIMITED, STRIDES PHARMA, INC., TORRENT PHARMA INC., TORRENT PHARMACEUTICALS LTD., ZYDUS PHARMACEUTICALS (USA) INC., CADILA HEALTHCARE LTD., 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

2021-1070

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

Decided: January 3, 2021

JANE M. LOVE, Gibson, Dunn & Crutcher LLP, New York, NY, argued for plaintiff-appellee. Also represented by PAUL E. TORCHIA, ROBERT TRENCHARD.

PAUL SKIERMONT, Skiermont Derby LLP, Dallas, TX, argued for defendants-appellants. Also represented by SARAH ELIZABETH SPIRES; MIEKE K. MALMBERG, Los Angeles, CA.

Before MOORE, *Chief Judge*, LINN and O'MALLEY, *Circuit Judges*.

Opinion for the court filed by *Circuit Judge* O'MALLEY.

Dissenting opinion filed by *Chief Judge* MOORE

O'MALLEY, *Circuit Judge*.

HEC Pharm Co., Ltd. and HEC Pharm USA Inc. (collectively, "HEC") appeal from a district court bench trial in which the court found that a patent assigned to Novartis Pharmaceuticals Corp. ("Novartis"), U.S. Patent No. 9,187,405 ("the '405 patent"), is not invalid and that HEC's Abbreviated New Drug Application ("ANDA") infringes. HEC argues that the district court erred in finding that the '405 claims do not fail the written description requirement of 35 U.S.C. § 112(a). Because we do not discern any clear error in the district court's decision, we affirm.

I. BACKGROUND

Novartis markets a 0.5 mg daily dose of fingolimod hydrochloride under the brand name Gilenya. The medication is used to treat relapsing remitting multiple sclerosis ("RRMS"), a form of multiple sclerosis ("MS"). MS is a debilitating immune-mediated demyelinating disease in which the immune system attacks the myelin coating the nerves in the central nervous system. Most MS patients initially present as RRMS patients, but many eventually develop a secondary progressive form of MS, causing them to experience growing disability. There is currently no cure for MS. The disease is managed by reducing or preventing relapses and thereby slowing disability.

HEC filed an ANDA seeking approval to market a generic version of Gilenya. Novartis sued, alleging that HEC's ANDA infringes all claims of the '405 patent.[1]

A. The '405 Patent

The '405 patent claims methods to treat RRMS with fingolimod (also known as FTY720 and 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol in the '405 patent) or a fingolimod salt, such as fingolimod hydrochloride (also known as Compound A in the '405 patent), at a daily dosage of 0.5 mg without an immediately preceding loading dose. '405 patent col. 12 ll. 49–55.

A loading dose is a higher than daily dose "usually given 'as the first dose.'" J.A. 27 (¶ 63) (quoting J.A. 23125 (Tr. 547:12–18) and citing J.A. 23344 (Tr. 766:4–6)). Both parties' experts agreed with this definition. J.A. 23125 (547:12–18) (HEC's expert, Dr. Hoffman, testifying that "a

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[1] Novartis sued several other defendants who had also filed ANDA applications. The cases as to those other defendants all settled or were stayed prior to trial, which proceeded only as to HEC.

loading dose is a higher-than-therapeutic level dose, usually given . . . as the first dose in order to get therapeutic levels up quickly . . . and it's usually for more acute situations"); J.A. 23344 (Tr. 766:4–6) (Novartis's expert, Dr. Steinman, agreeing that "a loading dose is a higher-than-daily dose"). It is undisputed that loading doses were well-known in the medical field generally and in the prior art. And the experts in this case agree that loading doses are used for some medicaments used in connection with MS.

The '405 patent has six claims. Claim 1 of the '405 patent recites:

> 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.

Claims 3 and 5 are similar but are directed to a "method of treating" RRMS and a "method of slowing progression of" RRMS, respectively, rather than a "method for reducing or preventing or alleviating relapses in" RRMS. *Id*. col. 12 ll. 59–64, col. 13 ll. 1–6. Claims 2, 4, and 6 are dependent claims that limit the methods of claims 1, 3, and 5, respectively, to administration of 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride, i.e., fingolimod hydrochloride. *Id*. col. 12 ll. 56–58, col. 12 ll. 65–67, col. 13 ll. 7–9.

The '405 patent was filed on April 21, 2014. It claims priority to a British patent application that was filed on June 27, 2006. The parties, for the most part, focus their discussion on the specification of the '405 patent, despite HEC's argument that the inventors did not possess the invention *as of the 2006 priority date*. HEC's argument that the 2006 application does not contain adequate written

description of the '405 claims requires reference to the 2006 application itself. Thus, we find it necessary to look to the specification of the 2006 priority application, despite the parties' failure to fully explain the contents of that application. Although the specifications are different from each other, they are, in all aspects relevant to this appeal, substantively similar.

The specifications of the '405 patent and the 2006 priority application both describe the use of a class of S1P receptor modulators, including fingolimod, to treat or prevent "neo-angiogenesis associated with a demyelinating disease, e.g. multiple sclerosis." '405 patent col. 1 ll. 5–8; J.A. 23751. The specifications each identify fingolimod hydrochloride (Compound A) as a particularly preferred compound within the class of S1P receptor modulators. '405 patent col. 8 ll. 17–30; J.A. 23759–60.

Both specifications describe the results of an Experimental Autoimmune Encephalomyelitis ("EAE") experiment. '405 patent col. 10 ll. 32–col. 11 ll. 2; J.A. 23762–63. In the EAE experiment, a disease that mimics RRMS was induced in Lewis rats.[2] The rats suffered acute disease within 11 days after immunization, with almost complete remission around day 16 and relapse around day 26. The specifications report that an S1P receptor modulator, e.g., Compound A (fingolimod hydrochloride) "significantly blocks disease-associated neo-angiogenesis when administered to the animals at a dose of from 0.1 to 20 mg/kg p.o."[3] '405 patent col. 10 ll. 61–64; J.A. 23763. They further report that disease relapse was completely inhibited in rats to which Compound A was "administered daily at a dose of

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[2] Lewis rats are inbred laboratory rats used to study disease. *Inbred Rats*, CHARLES RIVER, https://www.criver.com/sites/default/files/resources/InbredRatsDatasheet.pdf (last visited November 5, 2021).

[3] P.o. indicates oral administration.

0.3 mg/kg" or "administered p.o. at 0.3 mg/kg every 2nd or 3rd day or once a week." '405 patent col. 10 ll. 64–col. 11 ll. 3; J.A. 23763.

Both specifications then describe a prophetic human clinical trial ("Prophetic Trial").[4] '405 patent col. 11 ll. 3–38; J.A. 23763–64. The Prophetic Trial describes a trial in which RRMS patients would receive 0.5, 1.25, or 2.5 mg of an S1P receptor modulator, e.g., Compound A (fingolimod hydrochloride), per day for two to six months. '405 patent col. 11 ll. 8–14; J.A. 23763. The specifications do not mention a loading dose associated with the Prophetic Trial. '405 patent col. 11 ll. 8–14; J.A. 23763.

Both specifications then describe a wide range of potential dosages, which "will vary depending upon, for example, the compound used, the host, the mode of administration and the severity of the condition to be treated." '405 patent col. 11 ll. 20–24; J.A. 23764. Those potential dosages include a "preferred daily dosage range [of] about from 0.1 to 100 mg" and "a dose of 0.5 to 30 mg [of Compound A] every other day or once a week." '405 patent col. 11 ll. 24–38; J.A. 23764.

B. The District Court Proceedings

After a four-day bench trial, the district court found that HEC's ANDA product would infringe claims 1–6 of the '405 patent. The court also found that HEC had not shown that the '405 patent is invalid for (1) insufficient written description for the no-loading-dose limitation and for the

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[4] Prophetic trials explain how a drug would be administered and how a patient given that drug should be monitored in a clinical trial. Prophetic trials are not clinical trials that are performed; they are merely described on paper. Prophetic trials are sometimes used in patent applications because clinical trials are expensive and time consuming.

claimed 0.5 mg daily dose or (2) anticipation. HEC appeals the district court's findings as to written description for the 0.5 mg daily dose and no-loading-dose limitations.

With respect to the written description for the claimed 0.5 mg daily dose, the district court found that a skilled artisan would understand that the inventors possessed a 0.5 mg daily dose based on one of the successful doses in the EAE experiment results, 0.3 mg/kg weekly. The court credited the testimony of two of Novartis's expert witnesses, Dr. Lawrence Steinman, M.D., and Dr. William Jusko, Ph.D., to make the leap from a 0.3 mg/kg weekly rat dosage to a 0.5 mg daily human dosage. The court noted that the 0.5 mg daily dose is also illustrated in the Prophetic Trial. The district court concluded that there was sufficient written description for the 0.5 mg daily dosage limitation.

With respect to the written description for the "absent an immediately preceding loading dose" limitation, the district court again found sufficient written description in the EAE model and the Prophetic Trial. Neither the Prophetic Trial nor the EAE model recite a loading dose. The district court found that the "Prophetic Trial describes giving a 'daily dosage of 0.5 . . . mg' fingolimod to treat RRMS, started 'initially.'" J.A. 26 (quoting '405 patent col. 11 ll. 8–13). The court found, crediting expert testimony, that, "[i]f a loading dose were directed, the Patent would say that a loading dose should be administered 'initially.'" J.A. 26 (citing J.A. 23334–35 (Tr. 756:16–757:8); J.A. 23441–42 (Tr. 863:22–864:18)). Similarly, the district court found that the "EAE example discloses a dosing regimen which does not involve a loading dose." J.A. 27 (citing J.A. 23345 (Tr. 767:3–5); J.A. 22793 (Tr. 215:16–21)). Finally, the court found that, while the patent describes alternate dosing regimens, such as "intermittent dosing," it does not describe administering those regimens with loading doses. J.A. 27. Thus, the district court concluded, "[t]he EAE model and the Prophetic Trial . . . indicate to a person of ordinary skill that the claimed invention did not include

the administration of a loading dose," and, thus, the patent provides sufficient written description of the negative limitation. J.A. 37–38.

HEC appeals. We have jurisdiction under 28 U.S.C. § 1295(a)(1).

II. DISCUSSION

On appeal, HEC challenges the district court's decisions concerning the '405 patent's written description of the 0.5 mg daily dose limitation and the no-loading-dose negative limitation. "Whether a claim satisfies the written description requirement is a question of fact that, on appeal from a bench trial, we review for clear error." *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1308 (Fed. Cir. 2015) (quoting *Alcon Rsch. Ltd. v. Barr Lab'ys, Inc.*, 745 F.3d 1180, 1190 (Fed. Cir. 2014)). Under the clear error standard, we will not overturn the district court's factual finding unless we have a "'definite and firm conviction' that a mistake has been made." *Nuvo Pharms. (Ireland) Designated Activity Co. v. Dr. Reddy's Lab'ys Inc.*, 923 F.3d 1368, 1376 (Fed. Cir. 2019) (quoting *Scanner Techs. Corp. v. ICOS Vision Sys. Corp. N.V.*, 528 F.3d 1365, 1374 (Fed. Cir. 2008)).

The written description requirement is found in section 112 of the patent statute, which provides that the patent's specification must contain "a written description of the invention, and of the manner and process of making and using it."[5] 35 U.S.C. § 112(a). A specification that "reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date" has adequate written description of the claimed invention. *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010). "[T]he test requires an objective inquiry into the four corners of the

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[5] 35 U.S.C. § 112(a) also contains the separate "enablement" requirement, which is not at issue in this appeal.

specification from the perspective of a person of ordinary skill in the art." *Id*.

HEC challenges the district court's decisions concerning the '405 patent's written description of two limitations: the 0.5 mg daily dose limitation and the no-loading-dose negative limitation.

Despite arguing that the inventors did not possess the claimed subject matter in 2006, HEC bases its arguments, not on the 2006 priority application's written description, but on the '405 patent's specification—leaving it to this court to independently search the 2006 priority application for written description of the claims. HEC's confusion is ultimately of no moment, as we find that the claims have adequate written description support in portions of the '405 specification which also appear in the 2006 priority application.[6]

A. Written Description for the Dosage Limitation

HEC argues that, as of the 2006 priority date, the inventors did not possess a 0.5 mg daily dose of fingolimod. It argues that, as of that date, 0.5 mg/day was considered too low to be effective to treat RRMS. It describes Novartis's calculation of the 0.5 mg/day human dose as derived

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[6] Both parties wrongly assume that, if the 2006 priority application lacks sufficient written description of the '405 patent's claims, those claims are invalid. If the 2006 priority application lacks sufficient written description for the '405 patent's claims, the '405 patent's claims are not automatically rendered invalid; they are merely deprived of the 2006 priority date. *See* 35 U.S.C. § 119; s*ee also Paice LLC v. Ford Motor Co.*, 881 F.3d 894, 906 (Fed. Cir. 2018) ("For claims to be entitled to a priority date of an earlier-filed application, the application must provide adequate written description support for the later-claimed limitations.").

from the lowest disclosed dose in the rat EAE model described in the specification as "undisclosed mathematical sleights of hand." Appellant's Br. 7. And it argues that the Prophetic Trial, which lists a 0.5 mg daily dose along with two other dosages, does not provide sufficient written description of the 0.5 mg dose. Finally, it asserts that "blaze marks" directing a skilled artisan to the 0.5 mg daily dose are absent from the '405 patent.

We do not find HEC's arguments convincing. The Prophetic Trial and the EAE model provide sufficient written description to show that, as of the priority date, the inventors possessed a 0.5 daily fingolimod dosage as claimed in the '405 patent. The Prophetic Trial describes dosing RRMS patients with fingolimod hydrochloride at daily dosages of 0.5, 1.25, or 2.5 mg. '405 patent col. 11 ll. 8–16. The Prophetic Trial's disclosure of two other dosages does not detract from the written description of the claimed dose. Nor do disclosures of dosage ranges in other areas of the specification lead away from the claimed dose.

The rat EAE model describes additional information which provides further written description for the 0.5 mg/day limitation. The EAE model describes a dosage of 0.3 mg/kg per week as effective to "fully block[] disease-associated angiogenesis and completely inhibit[] the relapse phases." '405 patent col. 10 ll. 64–col. 11 ll. 2. The district court credited the testimonies of Dr. Steinman and Dr. Jusko to arrive at the claimed 0.5 mg/day human dosage from the EAE experiment's 0.3 mg/kg per week rat dosage. Those experts both testified that a skilled artisan would have converted the lowest daily rat dose described in the EAE experiment (0.3 mg/kg weekly) to a daily dose (0.042 mg/kg daily). J.A. 24 (citing J.A. 23325–26 (Tr. 747:6–748:19); J.A. 23443 (Tr. 865:12–24); J.A. 23482 (Tr. 904:2–18)). The district court found, again based on expert testimony, that a skilled artisan "would immediately recognize that 0.3 mg/kg weekly (0.042 mg/kg daily) in rats" is approximately 60% lower "than the lowest known effective

dose in the prior art (0.1 mg/kg daily)." J.A. 24–25 (citing J.A. 23440–41 (Tr. 862:25–863:21)). It found that a skilled artisan "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." J.A. 25 (citing J.A. 23443–45 (Tr. 865:4–867:4); J.A. 23480–85 (Tr. 902:17–907:8)). It further found that a skilled artisan "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." J.A. 25 (citing J.A. 23356–57 (Tr. 778:25–779:14)).

HEC attacks the expert testimony underlying the district court's determination that the EAE experiment describes a 0.5 mg daily human dose as "undisclosed mathematical sleights of hand." Appellant's Br. 7. We disagree. A "disclosure need not recite the claimed invention *in haec verba*." *Ariad*, 598 F.3d at 1352. The disclosure need only "clearly allow persons of ordinary skill in the art to recognize that the inventor invented what is claimed." *Id.* at 1351. To accept HEC's argument would require us to ignore the perspective of the person of ordinary skill in the art and require literal description of every limitation, in violation of our precedent. We find no clear error in the district court's reliance on expert testimony in finding description of the 0.5 mg daily human dose in the EAE experiment results.

We also reject HEC's argument that the '405 patent does not have necessary "blaze marks" pointing to the 0.5 mg daily dose. "Blaze marks" directing an investigator of ordinary skill in the art to the claimed species from among a forest of disclosed options are not necessary in this case. In cases where the specification describes a broad genus and the claims are directed to a single species or a narrow subgenus, we have held that the specification must contain "'blaze marks' that would lead an ordinarily skilled investigator toward such a species among a slew of competing

possibilities." *Novozymes v. DuPont Nutrition Biosciences APS*, 723 F.3d 1336, 1349 (Fed. Cir. 2013).

"Blaze marks" are not necessary where the claimed species is expressly described in the specification, as the 0.5 mg daily dosage is here. *See, e.g.*, *Snitzer v. Etzel,* 465 F.2d 899, 902 (C.C.P.A. 1972) (finding that interference counts directed to the activation of a glass laser with trivalent ytterbium ions were adequately described by a specification listing fourteen materials which may be used as active laser ingredients, including trivalent ytterbium, and noting that "there would seem to be little doubt that the literal description of a species provides the requisite legal foundation for claiming that species"). The '405 patent does not contain the laundry-list-type disclosures that we have found require guidance to direct a skilled artisan to the claimed species—it contains the Prophetic Trial listing three doses, 0.5, 1.25, and 2.5 mg/day. While other sections of the specification disclose larger ranges of potential doses for S1P receptor modulators, e.g., 0.1 to 100 mg/day doses, those disclosures do not diminish the literal description of the 0.5 mg/day dose in the Prophetic Trial. All described dose ranges include the 0.5 mg/day dose. And smaller dosage ranges, such as 0.5–30 mg/day, are disclosed for fingolimod hydrochloride. Even if blaze marks were required in this case, the Prophetic Trial and 0.5–30 mg/day dosage range would provide a skilled artisan more than sufficient guidance to direct them to the claimed 0.5 mg/day dose.

Much of HEC's argument is directed to its assertion that no one, including the inventors, knew that a 0.5 mg/day dose would be effective as of the 2006 priority date. That argument fails for two reasons. First, efficacy is not a requirement of the claims. The claims require only administration of a 0.5 mg/day dose for, *inter alia*, treatment purposes. The district court found that the purpose limitations are adequately described, and HEC has not appealed that finding. Thus, cases such as *Nuvo Pharms.*, 923 F.3d 1368, in which this court found that claims directed to an

amount of uncoated PPI that is *effective* to raise the gastric pH to at least 3.5 were not adequately described by a specification that "provides nothing more than the mere claim that uncoated PPI might work" where skilled artisans "would not have thought it would work," are distinguishable. *See id.* at 1381. Second, as explained above, the EAE model provides evidence that the inventors knew that a 60% lower dose would be effective.

For these reasons, we find no clear error in the district court's holding that the 0.5 mg/day dosage limitation is adequately described. The district court's holding is supported by the specification and ample expert testimony interpreting that specification.

B. Written Description for the Negative Limitation

HEC argues that there is no written description of the negative limitation because the '405 specification contains no recitation of a loading dose "or its potential benefits or disadvantages at all." Appellant's Br. 40. It further argues that the district court's finding of written description of the negative limitation within the '405 specification contradicts the district court's finding that Kappos 2006, which is similarly silent as to loading doses, does not anticipate the claims. We find both arguments unavailing.

It is well established that there is no "new and heightened standard for negative claim limitations." *Inphi Corp. v. Netlist, Inc.*, 805 F.3d 1350, 1356 (Fed. Cir. 2015). We are aware of no case that suggests otherwise. And, while HEC asserts that "[i]t is well-settled law that silence alone cannot serve as a basis for" a negative limitation, Appellant's Br. 41, HEC identifies no case that actually supports that proposition. To the contrary, we repeatedly have resisted imposition of heightened written description standards for negative limitations, such as that urged by HEC.

For example, in *Santarus, Inc. v. Par Pharmaceutical, Inc.*, we found that claims directed to a method of

treatment with a pharmaceutical composition containing no sucralfate were adequately described by a specification that explained that, although sucralfate is "possibly the ideal agent for stress ulcer prophylaxis," it was known to have occasional adverse effects. 694 F.3d 1344, 1350–51 (Fed. Cir. 2012). In *Santarus*, as in this case, there was expert testimony providing a person of ordinary skill's understanding of the patent specification. *See id.* at 1351. The expert testimony in *Santarus* showed that "a person of ordinary skill in this field . . . would have understood from the specification that disadvantages of sucralfate may be avoided by the [claimed] formulation." *Id.* We explained that "[n]egative claim limitations are adequately supported when the specification describes a reason to exclude the relevant limitation." *Id.* We did not hold that a specification *must* describe a reason to exclude a negative limitation. A specification that describes a reason to exclude the relevant negative limitation is but one way in which the written description requirement may be met.

In *In re Bimeda Research. & Development Ltd.*, we held that a claim that excluded a specific anti-infective, acriflavine, was not adequately described by a disclosure that was inconsistent with the exclusion of acriflavine but not other anti-infectives or antibiotics. 724 F.3d 1320, 1324 (Fed. Cir. 2013). The claim at issue in *Bimeda* was directed to a method of preventing mastitis in dairy cows by sealing the teat canal of a cow's mammary gland with a seal formulation that excludes acriflavine. Other claims in the same patent excluded all anti-infective agents. We noted that the patent repeatedly distinguished the invention as able to prevent mastitis without the use of antibiotics. Based on the written description's consistent description of the invention's non-antibiotic approach to preventing mastitis, we concluded that the patent's disclosure was "inconsistent with a claim which excludes acriflavine, but *not* the presence of other antiinfectives or antibiotics." *Id.* (citation and quotation marks omitted). We did not require that the

specification describe a reason to exclude acriflavine specifically, but, rather, found only that a negative limitation which is inconsistent with the disclosure is not adequately described.

In *Inphi*, we confirmed that the written description requirement is satisfied where "'the essence of the original disclosure' conveys the necessary information—'regardless of *how* it' conveys such information, and regardless of whether the disclosure's 'words [a]re open to different interpretation[s].'" 805 F.3d at 1354 (quoting *In re Wright*, 866 F.2d 422, 424–25 (Fed. Cir. 1989) (citation and internal quotation marks omitted)). We explained that "*Santarus* simply reflects the fact that the specification need only satisfy the requirements of § 112, paragraph 1 as described in this court's existing jurisprudence[.]" *Id*. at 1356. And we noted that the "'reason' required by *Santarus* is provided, for instance, by properly describing alternative features of the patented invention." *Id*. (citing *In re Johnson*, 558 F.2d 1008, 1019 (C.C.P.A. 1977)).

In *Inphi*, we found that substantial evidence supported the Patent Trial and Appeal Board's ("Board") finding that a negative limitation which had been added during prosecution ("DDR chip selects that are not CAS, RAS, or bank address signals") was adequately described by an original specification which did not expressly articulate a reason to exclude RAS and CAS signals. We found the Board's decision was supported by evidence of (1) standards set by the Joint Electron Device Engineering Council, a global standard setting body for the microelectronics industry, incorporated by reference in the patent, which specify that DDR signals, including CS, RAS, CAS, and bank address signals, are distinct from each other; (2) a table in the specification which excludes RAS and CAS signals; and (3) various passages from the specification, including a figure which distinguishes chip select signals, command signals (including RAS and CAS signals) and bank address signals. We concluded that the specification's disclosure of

alternative features was sufficient to satisfy the written description standard for the negative limitation. *Id*. at 1357.

In *Nike, Inc. v. Adidas AG*, we reiterated that *Santarus* did not create a heightened standard for written description of negative limitations. 812 F.3d 1326, 1348 (Fed. Cir. 2016), *overruled on other grounds by Aqua Prods., Inc. v. Matal*, 872 F.3d 1290 (Fed. Cir. 2017). We stated that negative limitations, like all other limitations, are held to "the customary standard for the written description requirement." *Id*. In *Nike*, we found a limitation of "flat knit edges," which Adidas characterized as a negative limitation, was adequately described by three figures in the specification depicting the claimed textile element which Nike's expert opined could be made using flat knitting in contrast to another figure's textile element which is formed using a circular knitting machine. *Id*. at1348–49.

Similarly, in *Erfindergemeinschaft Uropep GBR v. Eli Lilly & Co.*, Judge Bryson, sitting by designation in the Eastern District of Texas, explained that the law does not require that the disclosure explain a negative limitation. 276 F. Supp. 3d 629, 657–58 (E.D. Tex. 2017), *aff'd*, 739 F. App'x 643 (Fed. Cir. 2018). Judge Bryson explained, citing *Bimeda*, that "[w]hat is prohibited is a negative limitation that is contrary to the thrust of the invention." *Id*. at 658. He noted that "a patentee can choose to claim any particular embodiments identified in the specification and exclude others, without explanation, as long as the claim does not indicate to persons of skill that it covers embodiments inconsistent with, and therefore unsupported by, the disclosure." *Id*.

In asserting that "silence alone cannot serve as a basis for" a negative limitation, Appellant's Br. 41, HEC attempts to create a new heightened written description standard for negative limitations. In doing so, it ignores a central tenet of our written description jurisprudence—that the disclosure must be read from the perspective of a

person of skill in the art—as well as precedent stating that the disclosure need not describe a limitation *in haec verba*. *See, e.g.*, *All Dental Prodx, LLC v. Advantage Dental Prod., Inc.*, 309 F.3d 774, 779 (Fed. Cir. 2002) ("[T]he failure of the specification to specifically mention a limitation that later appears in the claims is not a fatal one when one skilled in the art would recognize upon reading the specification that the new language reflects what the specification shows has been invented." (citing *Eiselstein v. Frank*, 52 F.3d 1035, 1039 (Fed. Cir. 1995)); *see also Ariad*, 598 F.3d at 1351. In other words, context and the knowledge of those skilled in the art matter. And, as the Supreme Court has made clear, when assessing what the written description reveals to a skilled artisan, common sense also matters. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007) (holding that, in an obviousness analysis, "[r]igid preventative rules that deny factfinders recourse to common sense, however, are neither necessary under our case law nor consistent with it").

The dissent notes that the Manual of Patent Examining Procedure ("MPEP")[7] states: "The mere absence of a positive recitation is not a basis for an exclusion." MPEP § 2173.05(i). As the dissent puts it—"silence alone is insufficient." Dissent at 4. Both the MPEP and the dissent are correct in their statement of the law: the "*mere absence* of a positive recitation" is not enough and "silence *alone* is insufficient." But the dissent, like HEC, ignores that it is how a skilled artisan reads a disclosure that matters. Written description may take any form, so long as a skilled artisan would read the disclosure as describing the claimed invention.

Our case law makes clear that "[c]ompliance with the written description requirement is essentially a fact-based

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[7] The MPEP is not binding on this court but may be persuasive.

inquiry that will 'necessarily vary depending on the nature of the invention claimed.'" *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 963 (Fed. Cir. 2002) (quoting *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1562 (Fed. Cir. 1991)). The MPEP similarly provides for written description in various forms. In addition to stating that the "mere absence of a positive recitation" is not enough, the MPEP also correctly states that no specific form of disclosure is required and provides for implicit written description. MPEP § 2173.05(i) states that "a lack of literal basis in the specification for a negative limitation may not be sufficient to establish a *prima facie* case for lack of descriptive support." And MPEP § 2163 states that "newly added claims or claim limitations must be supported in the specification through express, *implicit*, or inherent disclosure." MPEP § 2163 (emphasis added). What is critical is how a person of skill in the art would read the disclosure—not the exact words used.

HEC and the dissent urge us to elevate form over substance by creating a new rule that a limitation which is not expressly recited in the disclosure is never adequately described, regardless of how a skilled artisan would read that disclosure. As we have several times before, we reject the invitation to create a heightened written description standard for negative limitations. As with all other limitations, the negative limitation here must be accompanied by an original disclosure which *conveys to a person of ordinary skill* that the inventor was in possession of the claimed invention. *See Ariad*, 598 F.3d at 1351. And, as in all other written description challenges, HEC was required to show by clear and convincing evidence that the negative limitation was not adequately described. The district court did not clearly err in finding that HEC failed to do so.

In determining that there is adequate written description of the negative limitation, the district court correctly, and quite carefully, conducted "an objective inquiry into the four corners of the specification from the perspective of

a person of ordinary skill in the art" as required by our precedent. *See Ariad*, 598 F.3d at 1351. We review the evidence cited by the district court below and discern no clear error in the court's analysis or conclusions.

The Prophetic Trial describes giving RRMS patients fingolimod hydrochloride "at a daily dosage of 0.5, 1.25 or 2.5 mg p.o." '405 patent col. 11 ll. 8–9. It further states that: "Initially patients receive treatment for 2 to 6 months." *Id.* col. 11 ll. 13–14. Dr. Steinman, one of Novartis's expert witnesses, testified from the perspective of a skilled artisan that, if the Prophetic Trial included a loading dose, the patent would explicitly state as much:

> "[T]here were two places where if there were going to be a loading dose, you would explicitly state it.
>
> . . . .
>
> So the first place one might explicitly say there was—there was a preceding loading dose is when you described the daily dosage, the reason being a loading dose would occur before the first daily dose.
>
> The second place is even more dramatic, because they say, "Initially patients received treatment for 2 to 6 months." So now they're really zooming in on Day 1, what is that treatment, it's a daily dose of 0.5.
>
> So there were two perfectly logical places that if there was going to be a loading dose, it would have been stated.
>
> . . . .
>
> That's where you would put it if you were going to give a loading dose.

J.A. 23343 (Tr. 765:2–25).

Similarly, Dr. Fred Lublin, Ph.D., another expert testifying for Novartis, testified that a person of skill in the art

"would have viewed the patent as a document, as a complete document, that should give you all the information you need to carry out the claims, and that information of having a loading dose is not there, and what's instead there is examples of daily dose, daily dose, daily dose." J.A. 22791 (Tr. 213:6–15). Dr. Lublin testified that a "loading dose is a greater than normal dose that you give until you return to a maintenance dose" and a loading dose is "not a daily dose." J.A. 22792 (Tr. 214:1–9). He further testified that "[o]ne would expect in a patent that if there was going to be a loading dose, it would be specified." J.A. 22793 (Tr. 215:5–8). And a third expert testifying for Novartis, Dr. Jusko, similarly testified that, from the perspective of a person of skill in pharmacology, the Prophetic Trial has a "specified initial regimen that does not include a loading dose." J.A. 23442 (Tr. 864:14–16).

The district court credited this expert testimony, as well as the testimony from HEC's own expert, Dr. Paul Hoffman, M.D., who agreed that "a loading dose is a higher-than-therapeutic level dose, usually given . . . as the first dose." J.A. 23125 (Tr. 547:14–18); J.A. 27. Based on that evidence, the court concluded that 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." J.A. 26. We discern no clear error in that finding. The district court further noted that the rat EAE experiment does not describe a loading dose. J.A. 26. It again credited the testimony of multiple expert witnesses who testified that the EAE model did not include a loading dose. J.A. 26. Dr. Jusko, in response to a question about whether there are any loading doses in the EAE model, stated: "Not that I'm aware of." J.A. 22793 (Tr. 215:16–21). Dr. Steinman similarly testified that no loading dose was used in the EAE experiment. J.A. 23345 (Tr. 767:3–5). HEC's own expert witness, Dr. Hoffman, testified that the EAE model does not talk about a loading dose. J.A. 23209 (Tr. 631:18–22).

Based on both the specification's disclosure of the rat EAE model and the ample expert testimony providing evidence of how a person of ordinary skill would read that disclosure, the district court concluded that the "EAE example discloses a dosing regimen which does not involve a loading dose." J.A. 27. Finally, the district court noted that, while the patent "describes alternative dosing regimens, like 'intermittent dosing,' [it] does not describe loading doses." J.A. 27.

The district court concluded that the "EAE model and the Prophetic Trial . . . both indicate to a person of ordinary skill that the claimed invention did not include the administration of a loading dose." J.A. 37–38. We are not left with the "definite and firm conviction" that the district court made a mistake in coming to this conclusion. *See Nuvo Pharms.*, 923 F.3d at 1376 (quoting *Scanner Techs.*, 528 F.3d at 1374). To the contrary, the district court's conclusion appears wholly correct. To arrive at the opposite conclusion would require us to disregard the perspective of a person of skill in the art—something our precedent simply does not allow. *See Ariad*, 598 F.3d at 1351.

We also find unpersuasive HEC's argument that the district court's written description decision contradicts its determination that the '405 patent is not anticipated by Kappos 2006. HEC notes that neither Kappos 2006 nor the '405 patent's specification explicitly state that a loading dose should not be administered. But HEC's argument ignores the differences between the two district court findings and ignores the differences between the disclosures of Kappos 2006 and the '405 specification.

As a granted patent, the '405 patent is presumed valid. Thus, it is also presumed to have a complete written description. *See Nat'l Recovery Techs., Inc. v. Magnetic Separation Sys, Inc.*, 166 F.3d 1190, 1195 (Fed. Cir. 1999) ("The presumption of validity includes a presumption that the patent complies with § 112."). No such presumption

applies to disclosures of a prior art reference that is not itself a granted patent, such as Kappos 2006. Further, the perspective of a person of skill in the art is important in both the written description and the anticipation inquiries. And, in this case, the district court credited the testimony of two expert witnesses, Dr. Lublin and Dr. Steinman, who testified that a person of skill in the art would not presume that the Kappos 2006 abstract was complete. J.A. 30 (citing J.A. 22782 (Tr. 204:12–19) (Dr. Lublin testifying that abstracts "have to by design" leave out information describing clinical trials); J.A. 23475 (Tr. 897:1–5) (Dr. Steinman testifying that "an abstract, like a press release, like any kind of announcement, is inherently incomplete," while "a publication and a patent are presumed complete")). Thus, although neither the '405 specification nor Kappos 2006 include the phrase "loading dose," it was not clear error for the district court to find that a skilled artisan would read the specification as not including a loading dose and would read Kappos 2006 as silent on the presence or absence of a loading dose.

Differences between the '405 patent's specification and Kappos 2006 justify the district court's findings that the specification describes the absence of a loading dose while Kappos 2006 does not anticipate that negative limitation. The specification includes the Prophetic Trial, which the district court found "describes giving a 'daily dosage of 0.5 . . . mg' fingolimod to treat RRMS, started 'initially.'" J.A. 26. The district court found that, "[o]n this record, starting with a daily dose plainly implies that there is no loading dose." J.A. 27. Kappos 2006 consists of two paragraphs describing a planned clinical trial and, with respect to dosing, states only that "[a]pproximately 1.100 patients . . . are being randomised in a 1:1:1 ratio to once-daily fingolimod 1.25 mg, fingolimod 0.5 mg, or placebo, for up to 24 months." J.A. 24723–24. Kappos 2006 nowhere says that the daily fingolimod dosage should be "initially" administered. Thus, differences between Kappos 2006 and the '405

patent justify the district court's conclusions that Kappos 2006 does not anticipate the claims and the '405 specification adequately describes the claims.

The dissent takes umbrage with the district court's finding that the "Prophetic Trial describes giving a 'daily dosage of 0.5 . . . mg' fingolimod to treat RRMS, started 'initially'" because the '405 patent says "[i]nitially, patients receive treatment for 2 to 6 months." Dissent at 6–7; J.A. 26; '405 patent col. 11 ll. 13–14. The dissent would find that the "word 'initially' is not modifying the daily dosage; it is modifying the initial length of treatment in this example." Dissent at 6–7. The dissent, thus, would substitute its own factual findings for those of the district court. But, if the 2–6 month "initial" dose does not differ in any way from the previously described daily doses, the language, used in context, must exclude a loading dose. As we have already explained, the district court did not clearly err in finding that the "Prophetic Trial describes giving a 'daily dosage of 0.5 . . . mg' fingolimod to treat RRMS, started 'initially.'" J.A. 26. And we are not free to substitute our own factual findings for those of the district court absent clear error because "a district court judge who has presided over, and listened to, the entire proceeding has a comparatively greater opportunity to gain the necessary 'familiarity with specific scientific problems and principles,' . . . than an appeals court judge who must read a written transcript or perhaps just those portions referenced by the parties." *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 574 U.S. 318, 319 (2015) (quoting *Graver Tank & Mfg. Co. v. Linde Air Prods. Co.,* 339 U.S. 605, 610 (1950)).

The dissent also asserts that, on this record, the term "daily dose" would not convey to a skilled artisan that no loading dose should be used. Dissent at 7–8. But the district court's decision did not rely only on the term "daily dose." Rather, as noted above, the district court found that "*starting* with a daily dose plainly implies that there is no loading dose," as a loading dose is a larger-than-daily dose. J.A. 27 (emphasis added). We need not, and do not, go

further than the district court to make findings about the term "daily dose." The dissent's assertion to the contrary and allegation that we "tease[] an entirely new claim limitation out of an entirely common term, relegating the legal determination of a term's meaning to the backseat of an expert's post-hoc rationalization" is, frankly, baffling. *See* Dissent at 8.

Written description in this case, as in all cases, is a factual issue. In deciding that the district court did not clearly err in finding written description for the negative limitation in the '405 patent, we do not establish a new legal standard that silence is disclosure, as the dissent asserts. Instead, we merely hold that, on this record, the district court did not clearly err in finding that a skilled artisan would read the '405 patent's disclosure to describe the "absent an immediately preceding loading dose" negative limitation.

III. CONCLUSION

For the foregoing reasons, we affirm the district court's decision.

AFFIRMED

United States Court of Appeals for the Federal Circuit

NOVARTIS PHARMACEUTICALS CORPORATION,
Plaintiff-Appellee

v.

ACCORD HEALTHCARE, INC., AUROBINDO PHARMA LTD., AUROBINDO PHARMA USA, INC., DR. REDDY'S LABORATORIES, INC., DR. REDDY'S LABORATORIES, LTD., EMCURE PHARMACEUTICALS LTD., 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 LIMITED, STRIDES PHARMA, INC., TORRENT PHARMA INC., TORRENT PHARMACEUTICALS LTD., ZYDUS PHARMACEUTICALS (USA) INC., CADILA HEALTHCARE LTD., 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

2021-1070

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

MOORE, *Chief Judge*, dissenting.

The majority dramatically expands a patentee's ability to add, years after filing a patent application, negative claim limitations that have zero support in the written description. By doing so, it contradicts our well-established precedent and nullifies the Patent Office's guidance in the Manual of Patent Examining Procedure (MPEP). I would reverse the district court's finding that there exists written description support as it is inconsistent with our established precedent. Silence is not disclosure.

I

"The hallmark of written description is disclosure." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (en banc). The description in the specification must clearly allow a skilled artisan to recognize that the inventor invented what is claimed. *Id.* The '405 patent contains no written description support for the limitation "absent an immediately preceding loading dose regimen." This negative limitation was added in response to an obviousness rejection during prosecution of the '405 patent's co-pending parent application. J.A. 23892–94. Claim 1:

> 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*.

There is no disclosure in the specification of preventing a loading dose. Loading doses—whether to be used or not—are never discussed. As the majority concedes, we have long held that silence cannot support a negative limitation; for if the specification is silent there is no evidence that the inventor actually possessed the invention. Maj. at 17 ("Both the MPEP and the dissent are correct in their statement of the law: the 'mere absence of a positive recitation' is not enough, and 'silence alone is insufficient.'"). "Negative claim limitations are adequately supported when the specification *describes a reason to exclude* the relevant limitation," such as by listing the disadvantages of some embodiment. *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1351 (Fed. Cir. 2012). In *Inphi Corp. v. Netlist, Inc.*, 805 F.3d 1350, 1356 (Fed. Cir. 2015), we explained that reciting alternative features of the patented invention may also suffice.[1] In *Nike, Inc. v. Adidas AG,* we again reiterated that the specification should indicate a reason to exclude. 812 F.3d 1326, 1348 (Fed. Cir. 2016). This law, our law, does not create a heightened standard for negative claim limitations; it simply requires some disclosure to demonstrate that the inventor was not, as in this case, ambivalent about loading doses.[2]

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[1] *Erfindergemeinschaft Uropep GBR v. Eli Lilly & Co.*, 276 F. Supp. 3d 629, 657–59 (E.D. Tex. 2017), consistent with *Inphi*, holds that when a patent discloses many alternatives, the claims are permitted to claim only some and exclude others. The specification here does not disclose alternatives (some with and some without loading doses).

[2] *In re Bimeda Research & Development Ltd.*, 724 F.3d 1320, 1323–24 (Fed. Cir. 2013), does not help the majority at all. The court simply held that, when the patent repeatedly emphasizes that the invention was "without

Following our clear precedent, the Patent Office's MPEP provides the following guidance: "The mere absence of a positive recitation is not a basis for an exclusion," i.e., silence alone is insufficient. MPEP § 2173.05(i). That remains true even if it would have been obvious to a skilled artisan to exclude the undisclosed feature. *Rivera v. Int'l Trade Comm'n*, 857 F.3d 1315, 1322 (Fed. Cir. 2017) ("The knowledge of ordinary artisans may be used to inform what is actually in the specification, but not to teach limitations that are not in the specification, even if those limitations would be rendered obvious by the disclosure.").

Nowhere in the patent does it say a loading dose should not be administered. Nowhere does it discuss alternatives (including or not including a loading dose). Nowhere does it give advantages or disadvantages of including a loading dose. Indeed, it provides no reason to exclude a loading dose. Even Novartis' expert, Dr. Lublin, agreed:

> Q: Nothing in the text of the specification of the '405 patent discloses a rationale for the negative limitation prohibiting an immediately preceding loading dose, correct?
>
> A: I don't believe so.

J.A. 22872–73. And all the experts agreed that loading doses are sometimes given to MS patients. *See* J.A. 22780 (Dr. Lublin explaining that loading doses have been used in trials of MS drugs and with fingolimod in particular); J.A. 22794; J.A. 23347–48 (Dr. Steinman, Novartis' second physician expert, acknowledging that loading doses are used in MS treatments); J.A. 23475 (Dr. Jusko, Novartis' pharmacology expert, testifying that fingolimod was given to transplant patients with a loading dose, and that he "could envision the possibility of starting with a loading

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using antibiotics," a claim which allows some antibiotics lacks written description support. *Id.*

dose"). The '405 patent provides nothing to signal to the public that the inventors possessed a treatment excluding a loading dose when a loading dose was a known possibility.

The patent is silent, eerily silent. Consistent with *Santarus, Inphi,* and *Nike*, there needed to be some discussion of loading doses in order to show that the inventors in fact invented this treatment method that is not just ambivalent to, but expressly excludes, a loading dose. This is not a heightened written description requirement; it is simply a written description requirement.

The district court relied on the disclosure's silence to support the negative loading dose limitation, reasoning that silence "would tell a person of skill that loading doses are excluded from the invention." J.A. 26 ¶ 61. We have rejected the notion that a skilled artisan's knowledge can speak for a mute specification. *See Rivera*, 857 F.3d at 1322. Here, the expert that the majority relies upon to supplement a silent disclosure concludes that a loading dose is excluded because the patent is silent on loading doses: "the patent [i]s a document, as a complete document, that should give you all the information you need to carry out the claims, and that information of having a loading dose is not there." Maj. at 19–20 (quoting J.A. 22791). If silence were sufficient then every later-added negative limitation would be supported as long as the patent makes no mention of it. This is a fundamental error of law.

Novartis explained its support for the no-loading-dose limitation as follows:

> Judge Linn: There is nothing in the patent that says treatment begins with the daily dose?
>
> Novartis: Ummm the prophetic example says treatment begins initially and treatment is the 0.5 mg daily dose so if that begins initially it excludes the possibility of a loading dose.

> ***
>
> Chief Judge Moore: The patent says "Initially, patients receive treatment for 2 to 6 months," and you believe I should construe that as initially there is no loading dose?
>
> Novartis: Yes, your honor a loading dose is excluded from that treatment.

Oral Argument at 35:30–37:13. The majority claims that the Prophetic Example in the specification describes "start[ing] 'initially'" by "giving a 'daily dose of 0.5 . . . mg.'" Maj. at 7; Maj. at 22 (same). This is a false and inaccurate quotation. The word "initially" does not precede or modify the daily dosage sentence; it follows it three full sentences later. To be clear, the patent does NOT say treatment begins initially with a daily dose. Here is the actual quote:

> 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.

'405 patent at 11:8–16. The word "initially" is not some complex, scientific term in need of expert explanation. It is basic English. The word "initially" is not modifying the daily dosage; it is modifying the initial length of treatment

in this example.[3] To the extent that the district court reached a fact finding to the contrary, it is inconsistent with the straight-forward, quite clear language of the patent and therefore clearly erroneous.[4]

Novartis also claims that the use of the term "daily dosage" itself would convey to a skilled artisan that no loading dose should be used. This is not only unsupported by the record; it is contradicted at every turn. First, the claim already said "daily dosage" before the negative limitation was added. It was allowed only after the applicants added the no loading dose limitation. J.A. 23903 (Examiner's rejection in parent application); J.A. 23892–93 (Applicant Response in same); *see also* Novartis Br. 11–12. The applicants explained they added the no-loading-dose limitation "to specify that the [daily dosage] cannot immediately follow a loading dose regiment. Applicants have made these amendments to further distinguish their claims from the disclosure of [the prior art]." J.A. 23892.[5] If daily already meant no loading dose, then there would have been no reason for the claims to recite both a "daily dosage" and the negative loading dose limitation. The same logic applies to

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[3] I note that even if the Prophetic Example were to be understood as not having included a loading dose that does not mean that loading doses must be prohibited (as the claims now require).

[4] Nothing about this analysis "substitute[s] . . . factual findings for those of the district court." Maj. at 23. Instead, it merely points out how it is *clear error* for the majority, district court, and Novartis to misquote the specification.

[5] Novartis stated during argument that this limitation was "added to *clarify* that the claim does not overlap with [the prior art]." Oral Argument at 21:34–41. This litigation claim cannot be reconciled with their own prosecution statements.

the specification, which only mentioned "daily dosage." This prosecution makes clear that neither the applicant nor the examiner believed that the use of the term "daily dosage" alone conveyed the absence of a loading dose.

There is no evidence that daily had a special meaning in the field of pharmacology. Daily is not a complex or complicated term of art that requires expert testimony to explain. The district court construed the claim term "daily dosage of 0.5 mg" to mean "the amount of drug that someone takes in a given day." J.A. 18670. Neither party argued the term excludes a loading dose. *Id.* And for good reason—it has a plain meaning, and the prosecution history shows it does not implicitly exclude a loading dose. Novartis backdoors a claim construction argument, arguing that "experts understood the patent's description of a 'daily dose' as exclusive of a loading dose," Novartis Br. 46, but it and the district court already defined daily dosage otherwise.

Rather than defend Novartis' reliance on the "daily dosage" language, the majority pivots to focus on the district court's statement that "*starting* with a daily dose plainly implies that there is no loading dose." Maj. at 23–24 (quoting J.A. 27). But that statement is just another example of the district court (and now the majority) rewriting the specification with expert testimony. The patent never says "starting with a daily dose," and the district court relied exclusively on expert testimony to support that finding. *See* J.A. 27 (citing J.A. 23344). But "[t]he knowledge of ordinary artisans may . . . not [be used] to teach limitations that are not in the specification[.]" *Rivera*, 857 F.3d at 1322. Novartis, and now the majority, teases an entirely new claim limitation out of an entirely common term, relegating the legal determination of a term's meaning to the backseat of an expert's post-hoc rationalization.

In fact, the district court found that a nearly identical disclosure in the prior art (Kappos 2006, a Novartis-supported study) did not anticipate because it failed to disclose the negative loading dose limitation. Kappos disclosed a study administering 0.5 mg fingolimod to RRMS patients "*once-daily* fingolimod for up to 24 months." J.A. 29–30 ¶ 72; J.A. 24724. The district court found Kappos 2006 did *not* meet the negative loading-dose limitation, reasoning that "[t]he failure to mention a loading dose does not . . . indicate that the dose was not present in the trial, but only that the presence or absence of a loading dose was not mentioned." J.A. 30 ¶ 74. A district court's "internally inconsistent factual findings," like those here, "are, by definition, clearly erroneous." *In re Sentinel Mgmt. Grp., Inc.*, 728 F.3d 660, 670 (7th Cir. 2013); *see also United States v. AT&T, Inc.*, 916 F.3d 1029, 1033 (D.C. Cir. 2019) (citing, e.g., *Anderson v. City of Bessemer, N.C.*, 470 U.S. 564, 575 (1985)) ("A finding may be clearly erroneous when it is illogical or implausible, [or] rests on internally inconsistent reasoning.").

The majority's attempts to distinguish Kappos 2006 from the '405 patent fall flat. Maj. at 21–23. To be sure, Kappos 2006 does not "say[] the daily fingolimod dosage should be 'initially' administered." *Id.* at 22–23. But neither does the '405 patent. The '405 patent uses the word initially to describe the *length of treatment*, not the *dosage*. And it is simply not correct that an issued patent is "presumed to have a complete written description." Maj. at 21. "The presumption of validity includes a presumption the patent complies with" the written description requirement. *Nat'l Recovery Techs., Inc. v. Magnetic Separation Sys., Inc.*, 166 F.3d 1190, 1195 (Fed. Cir. 1999). But it does not require presuming an issued patent is "complete," which would mean silence presumptively supports a negative limitation in *every* case. That presumption is contrary to our long-standing precedent, which the majority recognizes

(*see* Maj. at 17), and a gross expansion of the presumption of validity.

This specification is ambivalent as to loading doses in a field where, by all expert accounts, loading doses of fingolimod were sometimes used to treat MS. The inventors do not get to claim as their invention something they did not disclose in the patent. There are no fact findings here to defer to—the patent is silent as to loading doses. The district court relied upon that silence: "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." J.A. 26 ¶ 61. This is not a finding of fact; it is a misunderstanding of the law. An inventor cannot satisfy the written description requirement through silence. And when the majority concludes otherwise, it creates a conflict with our long-standing, uniformly-applied precedent including *Santarus*, *Inphi*, and *Nike*. While the negative limitation need not be recited in the specification *in haec verba*, there must be something in the specification that conveys to a skilled artisan that the inventor intended the exclusion: disadvantages, alternatives, inconsistencies, just something. This specification is entirely silent and ambivalent about loading doses. These inventors did not disclose treatment that must exclude a loading dose, and the district court's finding to the contrary is clearly erroneous. After this case, negative limitations are supported by a specification that simply never mentions them.

Appendix C

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. Dr. Paul Hoffman, M.D.

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

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[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

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[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

Appendix D

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NOVARTIS PHARMACEUTICALS CORPORATION,	:	
Plaintiff,	:	
v.	:	C.A. No. 18-1043-LPS
ACCORD HEALTHCARE INC., et al.,	:	
Defendants.	:	

MEMORANDUM ORDER

Having considered the parties' briefing (D.I. 358, 458, 514) and having conducted an evidentiary hearing and heard oral argument on June 21, 2019, **IT IS HEREBY ORDERED THAT** Plaintiff's motion for a preliminary injunction (D.I. 357) is **GRANTED**.

IT IS FURTHER ORDERED THAT the parties shall submit a joint status report by Friday, June 28, 2019. That status report shall address, in addition to anything else the parties wish to raise, (a) whether the trial date should be accelerated; (b) how long the parties are likely to need for their trial presentations; (c) the amount of bond the Court should require Plaintiff to post; and (d) whether any discovery disputes remain ripe and require judicial attention.

The Court's decision to grant the preliminary injunction was, as stated as the conclusion of the hearing, for the following reasons:

> First I want to note I carefully considered all the materials that were in the record, including the voluminous record that you all created before today and, of course, everything that was cited in court today. That includes, but is not limited to, the various declarations of the witnesses, the deposition testimony, many documents, and the testimony that I got to hear live today.

The legal standards I think are not disputed, but let me just try to quickly note them for the record.

A preliminary injunction, of course, is an extraordinary remedy that should be granted only in limited circumstances. Deciding whether to grant a preliminary injunction requires consideration of whether the moving party can prove the following. A reasonable likelihood of success on the merits, irreparable harm if the injunction is not granted, a balance of hardship tipping in its favor, and the injunction's favorable impact on the public interest. Although the factors are not applied mechanically, a movant must establish the existence of both of the first two factors to be entitled to a preliminary injunction.

In the context of this suit, which is a patent infringement action, with respect to the likelihood of success on the merits, Novartis as the moving party must show both, one, it is likely to prove that the proposed generic product will infringe the asserted patent claim on which the motion is based, and, two, that defendants' challenges to the validity of the patent lack[] substantial merit.

Having applied that law to the facts as best as I could, my decision is to grant the motion for a preliminary injunction. Let me try to explain why.

First, turning to likelihood of success on the merits, I find that Novartis has met its burden to demonstrate a likelihood of success on the merits. Infringement is not contested for purposes of the preliminary injunction motion, so I need not address it any further. The issue, of course, is invalidity, and on invalidity, I have made a preliminary assessment as I'm required to do on defendants' three challenges. Anticipation by Kappos 2006, lack of adequate written description, and lack of enablement or utility.

At one level I think it is fair to say that there is a "substantial question of patentability." [But] I don't think that that is a fair description when that phrase is used in the manner that I understand it to be pertinent to the preliminary injunction analysis. That is, I don't think that defendants' invalidity contentions as argued here today are frivolous. If I were to permit summary judgment practice in this case, the defendants' invalidity defenses might very well survive a summary judgment motion. It's even possible, despite what I'm about to say, that defendants might prevail on one or more of their invalidity theories after trial, but having considered the evidence and the arguments before me at

this stage, my finding is that defendants are not at all likely to prevail at trial on invalidity.

That is, I am persuaded by Novartis that at trial, defendants will likely fail to persuade me by clear and convincing evidence that the asserted claims of the '405 patent are invalid due to anticipation by Kappos 2006, or due to lack of adequate written description, or due to lack of enablement and utility.

Having made that finding, I believe that plaintiff has done what the law requires it to do on likelihood of success on the merits when confronted with a challenge to the validity of its patent at the preliminary injunction stage. That's my understanding of what the Federal Circuit has told us is the legal standard at this stage. For instance, in the *Titan Tire* decision, 566 F.3d at page 1372, a 2009 decision,[1] the Federal Circuit told us that what the Court must do is "determine whether it is more likely than not that the patent challenger will be able to prove at trial by clear and convincing evidence that the patent is invalid." And, again, my finding for reasons I'm going to now try to explain is for the plaintiff, applying that standard.

Highly relevant to my finding on likelihood of success on the merits is that the defendants have proposed the wrong person of ordinary skill in the art, the wrong POSA. I am persuaded instead by plaintiff that the PTAB's definition of a POSA is correct here. It is a team that includes not just a clinician, but also a pharmacologist. I've been using a shorthand here, as I hope you will appreciate. As a formal matter, I'm adopting the specific definition of a POSA proposed by the plaintiff.

I've reached this conclusion for at least the following reasons. The patent contains parts that would be best understood by a pharmacologist even though the claims are principally directed to treatment and therefore to a clinician.

For instance, a pharmacologist is needed to understand the link between the EAE discussion of the specification and human dosing. Some of the prior art listed on the face of the patent and considered by the PTO is . . . pharmacological work relating to fingolimod. The invention as a whole is directed to a team which would necessarily include a pharmacologist for all the reasons that plaintiff has given, which are all well supported in the record.

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[1] *Titan Tire Corp. v. Case New Holland, Inc.*, 566 F.3d 1372, 1379 (Fed. Cir. 2009).

Defendants did not present any evidence from a pharmacologist or from the perspective of a pharmacologist. Therefore, they did not provide any evidence from the perspective of a POSA. Their expert, Dr. Hoffman, candidly admitted he doesn't know how a pharmacologist would interpret the patent. This alone I think is likely a sufficient basis to find that defendants are not likely to prevail on their invalidity challenges at trial. But I am not resting my decision solely or even principally on my finding regarding a POSA.

I will now turn to the three specific invalidity defenses that defendants have argued, and I find again that defendants are likely to fail on all three of them at trial.

First, anticipation by Kappos 2006.

In order for Kappos 2006 to anticipate the claims of the '405 patent, it must contain every element of the claims, either expressly or inherently. Also, Kappos 2006 must be enabled.

The Court agrees with Novartis that defendants are unlikely to persuade the Court at trial that Kappos 2006 discloses the '405 claim limitations of treatment and no loading dose.

First regarding treatment, Kappos 2006 is a test, not a method of treatment. At its publication date, the .5 milligram dose of fingolimod had never been used on a human MS patient. Nobody knew it would be an effective treatment, and no clinician would have prescribed it for an RRMS patient, including candidly defendants' clinical expert, Dr. Hoffman.

Kappos 2006 was a test. It was a hypothesis. It does not disclose and does not anticipate the treatment limitations of the asserted claims of the '405 patent.

This is reflected in a great deal of evidence about, for example, ethical concerns and even opposition to testing such a low dose on human RRMS patients, including Dr. Lublin's own hospital refusing to participate in the study and the unusual futility analysis required after six months of the test.

All of this would in one form or another have been part of what a POSA knew about fingolimod and would be part of why a POSA would read Kappos 2006 as something other than a method of treatment.

So that limitation is missing and that's enough to defeat the Kappos 2006 anticipation defense, but I also agree that Kappos 2006 also does not exclude an immediately preceding loading dose, which is an express limitation of the asserted claims of the '405 patent.

It is undisputed that Kappos 2006 is silent on the matter of a loading dose. I am persuaded on the present record that . . . Defendants will fail to persuade me at trial by clear and convincing evidence that a POSA, that is the properly defined POSA, which includes a pharmacologist, would read the one-page, approximately 600-word abstract as inherently and necessarily excluding a loading dose.

. . .

Given my conclusions on Kappos 2006 not containing all of the limitations of the asserted claims, I don't need to decide today if Kappos 2006 is enabling. All I would say on that is that my sense at the moment is that plaintiff's analogy to our *GSK* case is a persuasive comparison, and [D]efendants' efforts to distinguish *GSK*, which only came up today, appear likely to fail.[2]

Turning next to the written description defense. Under 35 U.S.C., Section 112, a patent must convey with reasonable clarity to a POSA that the inventor was in possession of the claimed invention at the time of the application.

The Court agrees with Novartis, that defendants are unlikely to persuade the Court at trial that the inventors of the '405 patent were not in possession of the claimed invention at the time of the application.

The properly defined POSA would read the '405 patent to have an adequate written description. That POSA is again a team that includes a pharmacologist, and I am persuaded, it is unlikely defendants will persuade me that a pharmacologist would fail to understand what the inventors invented and what the inventors were disclosing.

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[2] *See GlaxoSmithKline LLC v. Glenmark Pharm. Inc., USA*, 2017 WL 8944995 (D. Del. May 2, 2017), *report and recommendation adopted*, 2017 WL 2290141 (D. Del. May 25, 2017); *see also GlaxoSmithKline LLC v. Teva Pharm. USA, Inc.*, 313 F. Supp. 3d 582, 598 (D. Del. 2018).

Although not necessary, the parties today both introduced evidence of what the inventors themselves testified to, and this evidence on the whole supports plaintiff's view that the inventors had possession of their invention.

A patent does not need to tell the full story or really even any story about how the inventors came to their invention, and it need not state things that a POSA would already know, including the prior art. Much of the defendants' attack on the supposed lack of adequate written description is really legal irrelevancies, therefore.

And the third defense, turning to that, the lack of enablement or utility defense. Very little was said about this defense in court today. It is addressed a little bit in the briefing.

To be enabling, a specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. It must have utility as well.

Although not entirely clear, it may be in this context that defendants are arguing. "If Kappos does not disclose the absence of a loading dose, neither does the patent, and thus, Novartis did not describe any method supporting of possession of a claim." To the extent defendants are making that argument either in this or any other context, I find that plaintiff has adequately demonstrated, as the Patent Office similarly found, that when read in its full context, a person of skill does understand the patent to preclude a loading dose.

The Court is persuaded by the evidence that a POSA may well read an abstract differently than they read a patent. While far from dispositive, I think it's worth noting that the title of the patent includes, "treating RRMS" while the abstract is called "design of a randomized placebo-controlled study," and then it goes on, but that's the end of the part I'm quoting.

Lastly, defendants argue, "Novartis and its expert cannot point to any portion of the specification that contains actual information supporting the claimed utility in human patients." This I disagree with. It is contradicted and persuasively so by the testimony of Dr. Jusko. That is, that a pharmacologist would, in fact, understand how the EAE studies relate to the stated human doses.

So that takes care of likelihood of success on the merits. Turning next to irreparable harm.

Novartis has [met] its burden to show that there's a reasonable likelihood that in the absence of a preliminary injunction, one or more and up to six generics will undertake an [at-risk] launch in August of this year, and as a result, Novartis will suffer immediate and substantial harm that cannot be remedied by money damages even if Novartis ultimately prevails at trial and obtains a permanent injunction. These harms include the likely massive and immediate price erosion in the market for oral treatment of RRMS.

After what might be as long as a year of generic competition by the time we get to trial and I get a post-trial opinion done, Novartis will not be able to raise the price back to where it is now, or to where it would have been at that post-trial date in the absence of defendants' at-risk infringement.

Therefore, even assuming the amount of what would by that point . . . be the amount of past damages . . . could, with some difficulty, . . . be calculated, future damages beyond that date would also have to be calculated. That may be impossible. And then at that point, defendants will argue that they should not have to compensate Novartis for those future damages, i.e., the damages following the permanent injunction for the life of the patent.

Novartis has also proven that the relevant market will be condensed for [reasons] including issues relating to the requirement of FDO and the potential impact an at-risk launch might have on the availability of FDO.

I'm also persuaded that Novartis will suffer an irreparable injury to its goodwill from an at-risk launch for reasons including that to try to make itself whole [(or as whole as possible should it prevail at trial after an at-risk launch)], Novartis would have to raise Gilenya prices back to the pre-infringement level. [B]ut if Novartis tries to do that, Novartis would [(in this scenario[,] unfairly)], be widely criticized, thereby suffering irreparable harm to its goodwill.

. . . I'm not going to go into any further detail about the evidence on irreparable harm. We discussed most of that. That's highly confidential evidence and the courtroom was closed. I've considered all of that and I am largely persuaded by all of the arguments that the plaintiff has made on irreparable harm, but I'm

not going to go into further detail on that. Instead I will just discuss some of the defendants' arguments against irreparable harm.

Defendants' principal argument against finding irreparable harm is that Novartis has brought the harm on itself and that it has within its control the ability to mitigate or prevent these harms. I am not persuaded by these arguments. . . . [D]efendants did not unreasonably delay bringing suit on the '405 patent. Novartis did nothing inequitable in waiting to bring suit until after it received all of the many paragraph 4 certifications and after the IPR was completed, especially because the '405 patent was one that was never eligible to trigger a 30-month stay under the Hatch-Waxman Act and because pediatric exclusivity on the '229 patent protected Novartis from any potentially infringing competition until August of 2019.

Now, Novartis's course of action was not the only reasonable course of action. It may not even have been the most reasonable course of action.

For instance, it's far from clear to me that I would have necessarily stayed proceedings on the '405 patent during the pendency of the IPR if I had been asked, but I was never asked. But the important point for today is that there was nothing wrong with what Novartis did. Novartis's actions and failure to sue sooner do[] not undermine its showing of irreparable harm. I entirely disagree with defendants' contention that none of us should be here today.

I also do think that defendants may well have been able to force the issue of the validity of the '405 patent earlier through a declaratory action. It may be that it would have been dismissed for lack of standing. I don't have to decide that now. Again, nobody asked me. But I think it is pertinent that defendants did not try.

Defendants have also contended that Novartis itself believes the '405 patent is invalid and had planned for and prepared to deal with event[ual] generic competition.

I'm not persuaded that Novartis believes the '405 patent is invalid, or that this belief somehow explains how Novartis has approached litigating the '405 patent[.] [A]nd the fact that Novartis is preparing, as best as it can, to deal with legitimate generic competition when it arrives does not mean that Novartis

should be confronted with premature [(likely infringing)] generic competition.

That's all I have to say on irreparable harm.

Turning, finally, to balance of harms and the public interest. I find again that Novartis has met its burden. Both of these factors, too, favor the relief that I am granting.

Defendants stand to lose the opportunity to earn on the order of $50 million collectively by not being able to compete over approximately the next year whereas Novartis will irreparably lose a market in which they sell approximately $1.8 billion of drugs [each] year. To me, that balance clearly favors Novartis under the circumstances.

I also think that while consumers would, of course, benefit from lower prices, there may be a corresponding harm in this particular market given the possible adverse impact on FDO services.

Further, the public has an interest in protecting valid patent rights and in maintaining incentives for the massive investments required for drug development.

Under the circumstances here, I think the balance of harms and the public interest favor the relief I am granting. Therefore, and for those reasons, I am granting the motion for a preliminary [injunction].

June 24, 2019
Wilmington, Delaware

HONORABLE LEONARD P. STARK
UNITED STATES DISTRICT JUDGE

Appendix E

NOTE: This order is nonprecedential.

United States Court of Appeals for the Federal Circuit

NOVARTIS PHARMACEUTICALS CORPORATION,
Plaintiff-Appellee

v.

ACCORD HEALTHCARE, INC., AUROBINDO PHARMA LTD., AUROBINDO PHARMA USA, INC., DR. REDDY'S LABORATORIES, INC., DR. REDDY'S LABORATORIES, LTD., EMCURE PHARMACEUTICALS LTD., 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 LIMITED, STRIDES PHARMA, INC., TORRENT PHARMA INC., TORRENT PHARMACEUTICALS LTD., ZYDUS PHARMACEUTICALS (USA) INC., CADILA HEALTHCARE LTD., 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

2021-1070

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

ON PETITION FOR PANEL REHEARING AND REHEARING EN BANC

Before MOORE, *Chief Judge*, NEWMAN, LOURIE, LINN[1], DYK, PROST, REYNA, TARANTO, CHEN, HUGHES, STOLL, and CUNNINGHAM, *Circuit Judges*.[2]

PER CURIAM.

O R D E R

Novartis Pharmaceuticals Corporation filed a combined petition for panel rehearing and rehearing en banc.

Law Professors and Civil Procedure Scholars David Hricik, Roger M. Baron, Lonny Hoffman, Jeffrey W. Stempel, Christa Laser, Emil J. Ali, and Dane Ciolino requested leave to file a brief as amici curiae which the court granted.

Intellectual Property Law Professors Martin J. Adelman, Emily Michiko Morris, Adam Mossoff, Kristen Osenga, Mark F. Schultz, Ted Sichelman, and Joshua Kresh also requested leave to file a brief as amici curiae which the court granted.

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[1] Circuit Judge Linn participated only in the decision on the petition for panel rehearing.

[2] Circuit Judge Stark did not participate.

A response to the petition was invited by the court and filed by HEC Pharm Co., Ltd and HEC Pharm USA Inc. The petition was referred to the panel that heard the appeal, and thereafter the petition for rehearing en banc was referred to the circuit judges who are in regular active service.

Upon consideration thereof,

IT IS ORDERED THAT:

The petition for panel rehearing is denied.

The petition for rehearing en banc is denied.

The mandate of the court will issue September 27, 2022.

FOR THE COURT

September 20, 2022
Date

/s/ Peter R. Marksteiner
Peter R. Marksteiner
Clerk of Court

Appendix F

NOTE: This order is nonprecedential.

United States Court of Appeals for the Federal Circuit

NOVARTIS PHARMACEUTICALS CORPORATION,
Plaintiff-Appellee

v.

ACCORD HEALTHCARE, INC., AUROBINDO PHARMA LTD., AUROBINDO PHARMA USA, INC., DR. REDDY'S LABORATORIES, INC., DR. REDDY'S LABORATORIES, LTD., EMCURE PHARMACEUTICALS LTD., 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 LIMITED, STRIDES PHARMA, INC., TORRENT PHARMA INC., TORRENT PHARMACEUTICALS LTD., ZYDUS PHARMACEUTICALS (USA) INC., CADILA HEALTHCARE LTD., 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

2021-1070

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

ON MOTION

Before MOORE, *Chief Judge*, LINN and HUGHES, *Circuit Judges*.

Circuit Judge LINN dissents in part.

PER CURIAM.

O R D E R

Novartis Pharmaceuticals Corporation ("Novartis") moves to stay the mandate pending a decision on a forthcoming petition for a writ of certiorari. Novartis separately moves for leave to seal the motion to stay mandate.

Upon consideration thereof,

IT IS ORDERED THAT:

(1) The motion to stay the mandate is denied.[1]

(2) The motion to seal is granted.

FOR THE COURT

September 27, 2022
Date

/s/ Peter R. Marksteiner
Peter R. Marksteiner
Clerk of Court

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[1] Circuit Judge Linn dissents from the denial of the motion to stay the mandate and would grant the alternative request to extend the mandate deadline by an additional three days.

Appendix G

US009187405B2

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

(10) **Patent No.: US 9,187,405 B2**
(45) **Date of Patent: Nov. 17, 2015**

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

(71) Applicants: **Peter C. Hiestand**, Austria (CH); **Christian Schnell**, Hesingue (FR)

(72) Inventors: **Peter C. Hiestand**, Austria (CH); **Christian Schnell**, Hesingue (FR)

(73) Assignee: **Novartis AG**, Basel (CH)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **14/257,342**

(22) Filed: **Apr. 21, 2014**

(65) **Prior Publication Data**

US 2014/0228446 A1 Aug. 14, 2014

Related U.S. Application Data

(60) Division of application No. 13/149,468, filed on May 31, 2011, now Pat. No. 8,741,963, which is a continuation of application No. 12/303,765, filed as application No. PCT/EP2007/005597 on Jun. 25, 2007, now abandoned.

(30) **Foreign Application Priority Data**

Jun. 27, 2006 (GB) 0612721.1

(51) **Int. Cl.**

A61K 31/13	(2006.01)
C07C 215/08	(2006.01)
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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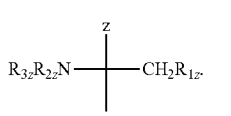
(Continued)

Primary Examiner — Kevin E Weddington
(74) *Attorney, Agent, or Firm* — Jim Lynch

(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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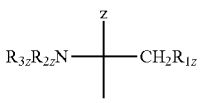
S1P RECEPTOR MODULATORS FOR TREATING RELASPING-REMITTING MULTIPLE SCLEROSIS

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.

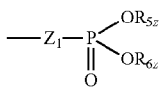
Sphingosine-1 phosphate (hereinafter "S1P") is a natural scrum lipid. Presently there are eight known S1P receptors, namely S1P1 to S1P8. S1 P receptor modulators are typically sphingosine analogues, such as 2-substituted 2-amino-propane-1,3-diol or 2-amino-propanol derivatives, e. g. a compound comprising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

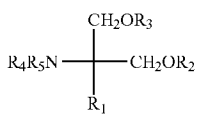
The lymphocyte homing property may be measured in following Blood Lymphocyte Depletion assay:

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 suhstituted hy 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

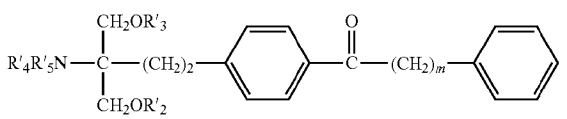
as a substituent C_{1-4}alkoxy, C_{2-4}alkenyloxy, C_{2-4}alkynyloxy, arylC_{1-4}alkyloxy, acyl, C_{1-4}alkylamino, C_{1-4}alkylthio, acylamino, (C_{1-4}alkoxy)carbonyl, (C_{1-4}alkoxy) carbonylamino, acyloxy, (C_{1-4}alkyl)carbamoyl, nitro, halogen, amino, hydroxy or carboxy, and

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

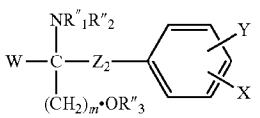


wherein m is 1 to 9 and each of R'_2, R'_3, R'_4 and R'_5, independently, is H, C_{1-6}alkyl or acyl,

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,

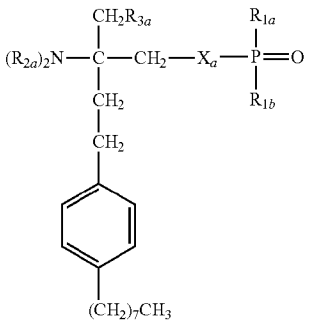
each of p and q, independently, is an integer of 1 to 20, with the proviso of $6 \le p+q \le 23$, m' is 1, 2 or 3, n is 2 or 3,

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,

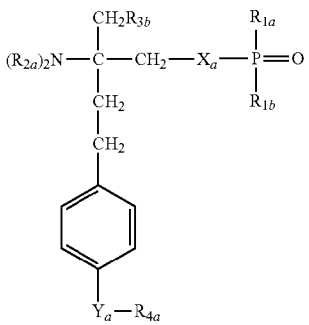
Compounds as disclosed in WO02/18395, e.g. a compound of formula IVa or IVb

IVa



or

IVb

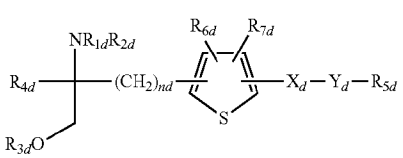


wherein X_a is O, S, NR_{1a} or a group $—(CH_2)_{na}—$, which group is unsubstituted or substituted by 1 to 4 halogen; n_a is 1 or 2, R_{1a} is H or (C_{1-4})alkyl, which alkyl is unsubstituted or substituted by halogen; R_{1a} is H, OH, (C_{1-4})alkyl or O(C_{1-4})alkyl wherein alkyl is unsubstituted 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 bydroxy, 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;

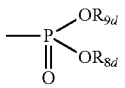
Compounds as disclosed in WO02/06268AI, e.g. a compound of formula V

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;

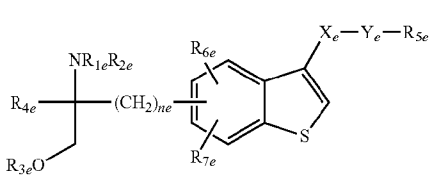
<group a> is halogen, lower alkyl, halogeno lower alkyl, lower alkoxy, lower alkylthio, carboxyl, lower alkoxycarbonyl, hydroxy, lower aliphatic acyl, amino, mono-lower alkylamino, di-C_{1-4}alkylamino, acylamino, cyano or nitro; and

<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

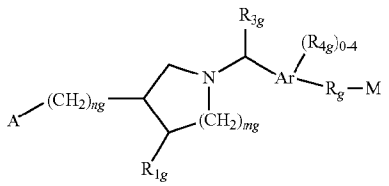


wherein R_{1e}, R_{2e}, R_{3e}, R_{4e}, R_{5e}, R_{6e}, R_{7e}, n_e, X_e and Y_e are as disclosed in JP-14316985;

or a pharmacologically acceptable salt, ester or hydrate thereof;

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

VII



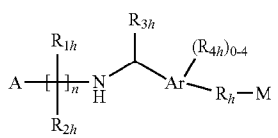
wherein

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

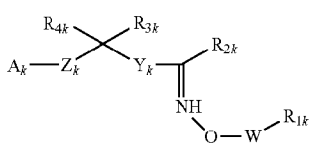


wherein Ar is phenyl or naphthyl; n is 2, 3 or 4; A is COOH, 1H-tetrazol-5-yl, PO_3H_2, PO_2H_2, —SO_3H or $PO(R_{5h})OH$ wherein R_{5h} is selected from C_{1-4}alkyl, hydroxyC_{1-4}alkyl, phenyl, —CO—C_{1-3}alkoxy and —CH(OH)-phenyl wherein said phenyl or phenyl moiety is optionally substituted; each 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.

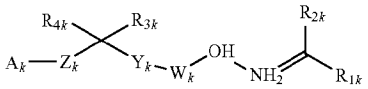
Compounds as disclosed in WO 04/103306A, WO 05/000833, WO 05/103309 or WO 05/113330, e.g. compounds of formula IXa or IXb

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.

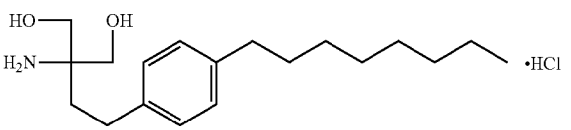
When in the compounds of formula I the carbon chain as R_1 is substituted, it is preferably substituted by halogen, nitro, amino, hydroxy or carboxy. When the carbon chain is interrupted by an optionally substituted phenylene, the carbon chain is preferably unsubstituted. When the phenylene moiety is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

* * * * *

Appendix H

No. 21-1070

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. REDDY'S LABORATORIES, INC., DR. REDDY'S 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 PHARMACEUTICALS INC., STRIDES GLOBAL PHARMA PRIVATE 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.

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

NONCONFIDENTIAL DECLARATION OF CHRISTOPHER VELLTURO, PH.D., IN SUPPORT OF PLAINTIFF-APPELLEE'S MOTION TO STAY THE MANDATE

September 23, 2022

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I, Christopher Vellturo, Ph.D., declare as follows:

I. INTRODUCTION AND ASSIGNMENT

1. I am an economist with extensive experience in the valuation of intellectual property and in the assessment of economic injury sustained as a result of patent infringement. Previously, I was asked by counsel for Novartis Pharmaceuticals Corporation to assess whether Novartis would suffer substantial and irreparable harm if the original Defendants in this matter were to launch "at risk" their allegedly infringing generic versions of Gilenya – Novartis's oral fingolimod drug for relapsing-remitting multiple sclerosis (RRMS) – and then subsequently withdraw their generic products from the marketplace as a result of further litigation. In that context, I previously submitted expert declarations and provided deposition testimony in the District Court in this case, in which I outlined my opinions that Novartis would indeed suffer substantial and irreparable harm in such a scenario.

2. During the course of this case's proceedings, I understand that on June 24, 2019, Judge Leonard P. Stark of the District of Delaware granted Novartis's motion for a preliminary injunction against Defendants' launch of a generic version of Gilenya.[1] In his ruling, Judge Stark cited three central elements contributing to his finding of likely irreparable harm to Novartis – 1) "massive and immediate price erosion in the market for oral treatment of RRMS;" 2) "the potential impact an at-

[1] *See* Case No. 1:18-cv-01043-KAJ, Dkt. 583 (D. Del. June 24, 2019).

risk launch might have on the availability of [First Dose Observation]," ("FDO"); and, 3) Novartis's "irreparable injury to its goodwill from an at-risk launch."[2] Subsequently, following a bench trial in March 2020 pertaining to alleged infringement of U.S. Patent No. 9,187,405 ("the '405 patent") by current Defendant-Appellant HEC Pharm Co., Ltd. and HEC Pharm USA Inc. (collectively, "HEC"), I understand that Judge Kent Jordan – to whom the case was transferred – entered a final judgment finding the '405 patent to be not invalid and finding HEC liable for induced and contributory infringement.

3. Since that judgment was entered, I understand HEC appealed the decision to a Federal Circuit panel, which affirmed the judgment in January 2022.[3] Most recently, I understand the Federal Circuit panel granted HEC's petition for rehearing, vacated its prior decision, and ultimately reversed the district court judgement. In this context, I understand Novartis is seeking to stay the Federal Circuit's corresponding mandate, which I understand would remove the existing injunction on HEC's launch and sale, and allow for launches of generic fingolimod products.

4. Presently, I have been asked to evaluate whether the issuance of the Federal Circuit mandate and subsequent launch of generic fingolimod by HEC

[2] *See id.*, 7.
[3] *See* Case No. 21-1070, Dkt. 41 (Fed. Cir. Jan. 3, 2022).

would cause Novartis substantial and irreparable harm in the event an appeal by Novartis to the Supreme Court resulted in a grant of *certiorari*, the reversal of the Federal Circuit's prevailing opinion, and the ultimate withdrawal of generic fingolimod from the marketplace. Because of the substantial overlap between the issues relevant to this question and those considered by Judge Stark when issuing his June 2019 preliminary injunction ruling, I have been asked to focus my assessment on whether and to what extent those elements of my prior assessment apply in the present context. I have also been asked to revisit certain other issues discussed in my previous declarations.

II. QUALIFICATIONS AND EXPERIENCE

5. I founded and am president of Quantitative Economic Solutions, LLC, a microeconomic consulting firm. I received a Doctor of Philosophy degree (Ph.D.) in Economics from the Massachusetts Institute of Technology in Cambridge, Massachusetts, in 1989. My fields of specialization include industrial organization and econometrics. My curriculum vitae, which lists my testimony for the last four years and my publications, is attached as Appendix 1.[4] As noted therein, my experience with respect to intellectual property in litigation and non-litigation

[4] QES is being compensated for my time spent on this matter at an hourly rate of $1,100, which is my customary rate. Payment is not contingent on the outcome of this matter. QES is also compensated for the time spent on this matter by persons working at my direction. Those rates are lower than my hourly rate.

settings is extensive. Industries that I have studied in this context include: pharmaceutical products, medical devices, over-the-counter medications and instruments, consumer products, computer hardware and software, semiconductors, and many others.

6. I have studied the pharmaceutical industry for more than 30 years. I have analyzed patent infringement damages issues, commercial success and relevant nexus, and irreparable harm, including from the "at-risk" launch of pharmaceutical products. I have also studied pharmaceutical merger reviews in the United States and abroad in private antitrust actions and in contract disputes. I have served as an expert in damages assessment, economics generally, statistics/econometrics (including survey design and implementation), and as an expert on the pharmaceutical industry in particular.

III. SUMMARY OF OPINIONS

7. In my prior February 19, 2019 and May 14, 2019 preliminary injunction declarations and in my March 8, 2019 deposition, I explained how generic entry at that time would cause Novartis irreparable harm, even if generics were presumed to subsequently exit the market as the result of further litigation results/rulings.[5] As

[5] *See* Case No. 1:18-cv-01043-KAJ, Dkt. 363 (D. Del. Feb. 19, 2019) ("Vellturo PI Declaration"); *id.*, Dkt. 517 (D. Del. May 14, 2019) ("Vellturo Reply PI Declaration"). Citations to the Vellturo PI Declaration incorporate the supporting evidence cited therein.

noted above, I understand Judge Stark cited in his June 24, 2019 ruling three central elements contributing to his finding of likely irreparable harm to Novartis. In this declaration, I conclude that these three central elements apply with equal or greater force in the present context, and thus, Novartis would incur the same or greater irreparable harms from an imminent generic fingolimod product launch as it would have in 2019. Namely, generic entry would still likely result in:

- substantial, immediate, and long-lasting price erosion for oral fingolimod products;
- the cessation of First Dose Observation ("FDO") support for new or returning fingolimod patients, resulting in material substitution away from both branded Gilenya and generic fingolimod products to other RRMS therapies; and
- significant and long-lasting harm to Novartis's goodwill in the medical community, including with third-party payers.

8. In this declaration, I summarize the key elements of my previous analysis along these dimensions, including relevant RRMS marketplace background, and discuss how intervening developments in this marketplace bear on my irreparable harm analysis. Ultimately, I find that if the Federal Circuit mandate were to issue and generic oral fingolimod products to launch – only to be subsequently enjoined following further proceedings in the litigation – none of these harms to Novartis could be fully quantified in a monetary damages award and, are, correspondingly, irreparable. Further, I find that HEC's launch of generic

fingolimod in particular would likely accelerate the launches of other generics, substantially deepening the resulting irreparable harms to Novartis.

9. Finally, I consider the potential harm to HEC and the impact on the public interest should the Federal Circuit's mandate be stayed and the injunction against HEC's launch remain in place. I find that, as in 2019, potential harm to Novartis associated with generic launch and subsequent generic withdrawal far outweighs total potential harm to all generic entrants, including HEC, associated with a stay of the mandate and later reversal. I also find that a stay of the mandate would serve the public interest in large part because Novartis would maintain its FDO support programs throughout the pendency of branded Gilenya's exclusivity period.

IV. MARKETPLACE AND ECONOMIC FACTS

10. In my previously submitted declaration, I provided background on marketplace and economic dynamics germane to my irreparable harm analysis.[6] In this section, I summarize those key marketplace and economic facts and provide relevant updates where applicable.

[6] *See* Vellturo PI Declaration, § III.

A. The Parties[7]

1. Novartis

11. Novartis Pharmaceuticals Corporation ("Novartis"), headquartered in East Hanover, New Jersey, operates as a subsidiary of Novartis AG and markets and sells various medicines and treatments directed to helping patients and improving patient care.

12. Novartis is an innovative drug company that makes continuous efforts to innovate and achieve additional regulatory approvals for its products. According to its 2021 annual report, Novartis AG spent $9.5 billion on R&D in 2021, amounting to 18.5 percent of net sales.[8]

13. One of Novartis's key products is Gilenya, which, upon its initial FDA approval in 2010, became the first orally administered treatment for relapsing-remitting multiple sclerosis (RRMS).[9] Novartis financial information demonstrates that Gilenya sales have been robust since its launch, having generated approximately $14 billion in sales in the U.S. from its initial launch in September 2010 through December 2021 on a net dollar sales basis (calculated as gross dollar sales less

[7] Unless otherwise noted, background facts about the parties are sourced from my review of the relevant parties' websites or their publicly available SEC filings.
[8] https://www.novartis.com/sites/novartiscom/files/novartis-annual-report-2021.pdf (Novartis 2021 Annual Report) at F-1.
[9] Vellturo PI Declaration, ¶ 16.

rebates, discounts, and allowances).[10] Gilenya has generated more than $1 billion in annual net dollar sales in every year from 2013 through 2021, qualifying Gilenya as a "blockbuster drug" for nine years running.[11] As of the second quarter of 2022, Gilenya remained one of Novartis's best-selling products.[12]

a. Gilenya's First-Dose Observation Requirement and Baseline Assessments[13]

14. In addition to other baseline medical assessments required before initiating Gilenya, Gilenya's labeled prescribing information includes a "First-Dose Monitoring" (also commonly referred to as "First Dose Observation" or "FDO") requirement.[14] According to Gilenya's label, all patients treated with Gilenya must be observed by a qualified medical professional for signs of bradycardia (slowing of

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[10] *Id.,* ¶ 17; https://www.novartis.com/sites/novartiscom/files/novartis-annual-report-2021.pdf (Novartis 2021 Annual Report) at p. F-25–F-27.

[11] Vellturo PI Declaration, ¶ 14; https://www.novartis.com/sites/novartiscom/files/novartis-annual-report-2021.pdf (Novartis 2021 Annual Report) at p. 57. A blockbuster drug is one that generates more than $1 billion in annual sales per year. *See* https://www.prnewswire.com/news-releases/in-pursuit-of-the-elusive-drug--the-billion-dollar-blockbuster-301157807.html.

[12] https://www.novartis.com/sites/novartis_com/files/q2-2022-media-release-en.pdf at 4.

[13] The background facts in this section regarding Gilenya's "FDO" requirement, Novartis's services and support network, and Gilenya's sales and marketing programs are sourced from my conversations with Joseph Gialanella, Executive Director of Product Strategy for Gilenya (as well as Novartis's branded MS medications Kesimpta and Mayzent), and Cristian Azcarate, Vice President of Patient & Specialty Services for Novartis's MS programs.

[14] https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/022527s031lbl.pdf

the heart rate) for at least 6 hours after the first dose.[15] Additionally, "[e]lectrocardiograms (ECGs) prior to dosing and at end of the observation period" are required and certain patients require additional cardiac monitoring and other tests.[16] The FDO requirement makes initiating treatment on Gilenya more burdensome and expensive than other RRMS treatments (which lack the FDO requirement).[17]

15. First Dose Observation is also required for patients who have previously been on Gilenya but have had a break of 14 or more days in their treatment.[18] Of the Gilenya patients undergoing FDO, the company estimates 20% are classified as undergoing "re-FDO."

b. **The Gilenya Go Program: Patient Services and Support Network**

16. To support Gilenya patients, Novartis has established an extensive support network known as the Gilenya Go Program, which is administered through what is referred to as the Gilenya "Hub."[19] Specifically, the Go Program provides a variety of services designed to simplify the onboarding process for new Gilenya

[15] *Id.*
[16] *Id.*
[17] Vellturo PI Declaration, ¶ 19.
[18] *Id.,* ¶ 20.
[19] *Id.,* ¶ 22.

patients, to assist with the treatment protocol for existing Gilenya patients, and to help ease financial and non-financial burdens for certain patients.

17. Among numerous other benefits, the Go Program provides assistance for patients to complete the baseline medical assessments and FDO required before beginning treatment on Gilenya. I understand that the Gilenya Go Program helps eligible patients identify locations for, schedules, coordinates, and, in many cases, offers to cover the cost of some or all of the baseline tests associated with beginning Gilenya treatment, including the FDO. The Go Program has assisted patients in expediting appointments with specialists to receive the assessments required to start Gilenya, avoiding prolonged wait-times for appointments that have become common during the COVID-19 pandemic.

18. Novartis provides baseline assessments and FDO services through the Novartis Access Network (NAN), a system of an in-home provider plus onboarding sites across the US. Novartis contracts with MarketDynamics, a provider of networks consisting of national field-based, in-home health care professionals and equipment to perform all baseline assessments and FDOs in the patient's home. Baseline assessments, including associated lab costs, and FDOs provided through the NAN are free of charge to eligible patients. A majority of Gilenya patients who

Percentage

complete their FDO do so through the NAN.[20] For example, in 2022 to date, [redacted]% of patients who completed their FDO did so through NAN.[21]

19. Novartis budgeted $[redacted] Dollar for 2022 for the Gilenya patient support services described above.[22] [redacted] Financial Information [redacted].

2. HEC and Potential Generic Entrants

20. I understand that HEC Pharm Co., Ltd. and HEC Pharm USA Inc. are Defendants-Appellants in this action. I further understand from counsel that there are over twenty other generic companies that could enter the marketplace upon issuance of the Federal Circuit mandate, [redacted] Settlement Agreements [redacted].[23] Specifically, with respect to these settled generics, [redacted] Settlement Agreements [redacted]

[20] Exhibit 1 at 6.
[21] *Id.,* at 14.
[22] *Id.,* at 8.
[23] Specifically, I understand that Novartis has entered into settlement agreements with Accord, Alembic, Alkem, Apotex, Aurobindo, Biocon, Bionpharma, Breckenridge, Dr. Reddy's Laboratories ("DRL"), Emcure/Heritage, Ezra, Glenmark, Hetero, Mylan, Prinston, Strides, Sun, Teva, Torrent, and Zydus.

[redacted].

According to the FDA's website, as of September 23, 2022, twelve of those companies have final FDA approval to launch generic versions of Gilenya.[24] Four more have tentative FDA approval,[25] and I am unaware of any reason why those four could not receive final FDA approval imminently.

21. These numbers are consistent with internal Novartis estimates concerning generic entry. [redacted]

Business Plans

[redacted][27] I note that this is an exceptionally large number of generic entrants, not present in a typical case.

[24] *See* https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm, search "fingolimod;" FDA, "Marketing Status Notifications Under Section 506I of the Federal Food, Drug, and Cosmetic Act; Content and Format: Guidance for Industry," Aug. 2020, at 2-3, 5-6 .

[25] *See* https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm, search "fingolimod."

[26] Exhibit 2 at 3.

[27] *Id.,* at 3.

B. Relevant Competitive Considerations in the Treatment of Relapsing-Remitting Multiple Sclerosis Treatments[28]

22. Although there is currently no cure for RRMS, there are numerous treatments that can reduce the frequency of relapses and delay disease progression or accumulation of disability.[29] These treatments, known as "disease-modifying therapies" (DMTs; alternatively, "disease-modifying medications" or "disease-modifying treatments"), may be classified based on how they are administered: injection treatments, infusion treatments, and oral treatments.[30] The oral treatment category where Gilenya falls has become increasingly crowded with other therapies: Aubagio, marketed by Sanofi Aventis US; Tecfidera and Vumerity, marketed by Biogen; Zeposia, marketed by Bristol Myers Squibb; Mayzent, marketed by Novartis; Mavenclad, marketed by Merck; Ponvory, marketed by Janssen; and Bafiertam, marketed by Banner Life Sciences. Other classes of DMTs, such as infusions (e.g. Ocrevus (marketed by Roche/Genentech) and Tysabri (marketed by Biogen)), also hold significant marketplace share.

23. DMTs may also be classified by mechanism of action. Those classes include Sphingosine-1-Phosphate ("S1P") modulators (e.g., Gilenya, Mayzent,

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[28] The background information in this section regarding the marketplace for RRMS treatments is sourced from conversations with Joseph Gialanella and Cristian Azcarate, in addition to documents cited in this section.

[29] Vellturo PI Declaration, ¶ 39.

[30] https://nms2cdn.azureedge.net/cmssite/nationalmssociety/media/msnationalfiles/brochures/brochure-the-ms-disease-modifying-medications.pdf.

Zeposia, Ponvory); anti-CD20 monoclonal antibodies (e.g., Kesimpta); interferon betas (e.g., Avonex and Extavia); glatiramer acetates (e.g., Copaxone); fumerates (e.g., Tecfidera); and some others that do not fit into any of these categories (e.g., Aubagio). In addition to the treatments currently available, other treatments are undergoing development and are expected to launch commercially in the coming years. For example, ublituximab, an anti-CD20 monoclonal antibody being developed by TG Therapeutics, is expected to enter the marketplace.[31] The FDA is expected to decide on ublituximab's approval at the end of 2022.[32]

24. In recent years, generic versions of two MS medications, Tecfidera (dimethyl fumarate) and Copaxone (glatiramer acetate), launched.[33] With the launch

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[31] https://multiplesclerosisnewstoday.com/experimental-treatments-for-ms/ublituximab-tgtx-1101/

[32] https://multiplesclerosisnewstoday.com/news-posts/2022/06/01/fda-decision-ublituximab-relapsing-ms-pushed-back-years-end/

[33] https://investor.mylan.com/news-releases/news-release-details/mylan-brings-critical-access-multiple-sclerosis-community (noting Mylan launched its generic version of Tecfidera (dimethyl fumarate) in August 2020); https://www.novartis.com/news/media-releases/sandoz-announces-us-launch-glatopatm-first-generic-competitor-copaxone-20mg (noting Sandoz launched Glatopa, its generic version of Copaxone (glatiramer acetate) in June 2015). Additional generic forms of Copaxone (glatiramer acetate) have been approved since October 2017. *See* https://www.nationalmssociety.org/About-the-Society/News/FDA-Approves-Two-New-Generic-Forms-of-Copaxone%C2%AE-(G; https://www.sandoz.com/news/media-releases/sandoz-announces-us-fda-approval-and-launch-glatopar-40-mgml-three-times-week.

of generic Tecfidera and Copaxone, there are now generic options available in multiple classes of RRMS DMTs.[34]

C. Pharmaceutical Industry Context

25. My 2019 declaration in support of Novartis's motion for preliminary injunction provided a comprehensive background on the U.S. pharmaceutical industry and the characteristics that are central to understanding the nature and breadth of irreparable harm likely to be suffered by Novartis in the event of an "at-risk" launch. These facts remain relevant in the present context.

26. As I explained, one characteristic of the pharmaceutical industry that is key to my analysis is the tiered cost structure of third-party payer ("payer") formularies. This structure is commonly used to discourage prescriptions for the branded drug – which is more expensive – by making the cost of the branded drug more expensive to the patient than the generic substitute. The diminished formulary coverage and disadvantaged pricing of the branded reference product commonly affect its sales relative to those of the generic product. In the MS marketplace in particular, payers are expected to start placing much greater pressure on branded drugs in the near future. For example, Business Plans

[34] Notably, this means that low-cost generic options of modern MS therapies are already available, which dampens the incremental value of HEC's potential generic oral fingolimod product from a public interest perspective.

[redacted].[35]

V. IRREPARABLE HARM ANALYSIS

27. I understand irreparable harm is economic harm for which subsequent monetary compensation or injunctive relief would be insufficient to fully compensate the patentee. In this section, I assess whether the irreparable harm that Novartis was likely to suffer as a result of "at-risk" launches and subsequent withdrawals of generic oral fingolimod products at the time of my February 2019 declaration is equally likely to occur in the present context.

28. As an initial matter, in my 2019 declaration in support of Novartis's motion for preliminary injunction, I assumed that were the defendants to have launched their generic oral fingolimod products "at risk," and then subsequently be required to withdraw them from the marketplace, they would have been on the market for approximately eight months to one year.

29. Here, I understand that relevant time frame for the irreparable harm inquiry is similar. Specifically, following the issuance of the Federal Circuit's mandate:

- I understand HEC would be permitted to launch into the U.S. marketplace immediately;

[35] Exhibit 2 at 3 [redacted] Business Plans [redacted].

- Several incremental generic manufacturers would likely follow suit, [redacted] Settlement Agreements [redacted];
- I understand any permanent injunction following further rulings by the Supreme Court would not issue until mid-2023 at the earliest, implying a potential launch period for the generics of almost one year.

30. As discussed in Section IV.A.2, I understand that a large number of generic manufacturers have final FDA approval for a generic fingolimod product and would be permitted to launch immediately following the issuance of the mandate. I further note that a straightforward application of applied game theoretic principles and economic behavior under uncertainty indicates that the other potential generic suppliers will be significantly more likely to enter if HEC elects to enter. Should the mandate issue, a decision by HEC not to enter would reveal important information as to HEC's belief as to its likelihood of prevailing in the appeal process (a belief based in private information HEC has that other generic suppliers do not) – namely, that HEC feels the likelihood of losing on appeal is sufficiently high that it elects not to launch. Seeing this action (actually, inaction) by HEC would alter the other generics' beliefs as to their potential exposure to infringement damages should they launch; namely, it materially increases their likelihood of facing exposure to those damages.[36] Conversely, if HEC were permitted to launch and did launch

[36] It is well recognized in applied game theory that potential entrants facing limited information sets will "update" their strategic choice of whether to launch to reflect new information that can be derived from the observed actions of incumbents or

despite the inherent risk of damages and/or being forced to remove its products from the market, the settled generics would be more likely to discount those same risks and launch themselves.[37]

31. Moreover, once HEC were to launch, other approved generics would have a substantial incentive to launch as quickly as possible given the inherent advantages associated with early entry by generic suppliers known as "first-mover advantage."[38] The first-mover dynamic is likely to incentivize quick, subsequent launches in two ways. First, the first-mover's advantage in capturing sales in the marketplace is materially impacted by the length of time in which they are the only generic on the market. A seminal 2008 paper on this topic by Yu and Gupta studied data on 49 molecules for which the branded drug lost patent exclusivity and faced

other potential entrants. *See e.g.,* Tirole, Jean: *The Theory of Industrial Organization (1st Ed.)*, § 9.1.

[37] [redacted] Settlement Agreements [redacted].

[38] *See, e.g.,* Grabowski, Henry and John Vernon, "Brand Loyalty, Entry, and Price Competition in Pharmaceuticals after the 1984 Drug Act," *Journal of Law and Economics*, Vol. 35, No. 2, October 1992, pp. 331-350; Caves, Richard E., *et al.*, "Patent Expiration, Entry, and Competition in the U.S. Pharmaceutical Industry," *Brookings Papers: Microeconomics*, 1991, pp. 1-66.

entries from generics during the 1992–2000 period and found that the longer the first generic entrant remains the only generic in the marketplace (i.e., before entry of the second generic), the greater the size of its advantage.[39] Accordingly, non-HEC generics will seek to prevent HEC from gaining such an advantage by limiting the time in which they are on the market alone. Second, the approved generics will have a material incentive to attain some portion of first-mover advantage themselves, as the second-to-market generic can themselves enjoy a significant advantage over subsequent entrants. The same paper by Yu and Gupta found that the second entrant indeed garnered significantly more share relative to the third in the studied examples.[40]

32. In this context and in light of Judge Stark's June 24, 2019 ruling, I focus my analysis on three primary elements that contributed to my initial conclusion that Novartis was likely to suffer irreparable harm following "at-risk" generic launches – 1) Price erosion in the marketplace for RRMS therapies; 2) The impact of generic launch on the availability of FDO; and 3) Harm to Novartis's goodwill. I find that Novartis would likely suffer all these same harms – to an equal or greater degree –

[39] Yu, Yu and Sachin Gupta, "Pioneering Advantage in Generic Drug Competition," *International Journal of Pharmaceutical and Healthcare Marketing*, October 2008 ("Yu and Gupta"), p. 29.
[40] *Id.,* p. 28.

were the Federal Circuit mandate to issue and HEC and additional potential generic entrants to launch their generic oral fingolimod products.

A. Jailbreak Scenario and Corresponding Price Erosion Effects

1. Prior Analysis

33. My 2019 analysis contemplated the launch of up to nine generic versions of branded Gilenya (with five defendants having received tentative FDA approval and the remaining four generics awaiting tentative approval) and explained that it is well established that the ultimate magnitude of price erosion on a branded product following generic entrant is heavily dependent on the total number of entrants. [redacted] Business Plans [redacted][41] Projected discounts off branded WAC increase significantly as additional generics enter the market, increasing to [redacted] percent with two generics, [redacted] percent with three generics, [redacted] percent or greater with five or more generics.[42] Percentages

34. Indeed, such erosion is entirely logical, as generic manufacturers cannot, by definition, differentiate their products in any way other than via pricing. I thus concluded that with up to nine potential "at-risk" entrants, the resulting price

[41] Vellturo PI Declaration, ¶ 61.
[42] *Id.*

erosion in the oral fingolimod marketplace would have been drastic. Documents provided by the generic manufacturers at the time further illustrated this likelihood, [redacted] Financial Information [redacted].[43]

35. In light of such generic prices, third-party payers likely would have threatened to remove a branded product from its historical formulary position and shift patient volume to generics at a significantly lower cost, especially given payers had additional options for RRMS treatments.[44] Thus, Novartis would have faced the tradeoff between maintaining Gilenya's effective price (and associated per-unit revenues) and sacrificing its established formulary presence (and, correspondingly, significant sales volumes).

36. Moreover, I explained that Novartis would have likely been unable to successfully restore pre-generic pricing following a subsequent generic withdrawal for multiple key reasons. First, there would likely have been contractual restraints to doing so, both due to the duration of typical Gilenya contracts, and due to specific negotiation provisions included in those contracts. Second, leaving aside the distinct contractual issues, Novartis would have been limited in its ability to extract higher prices from payers without straining their relationship with these key customers. I

[43] *Id.*, ¶ 64.
[44] *Id.*, ¶¶ 65–68.

further noted that Novartis considered a variety of strategic options to soften the impact of generic entry on its operations but did not expect to be able to entirely stem its losses.[45]

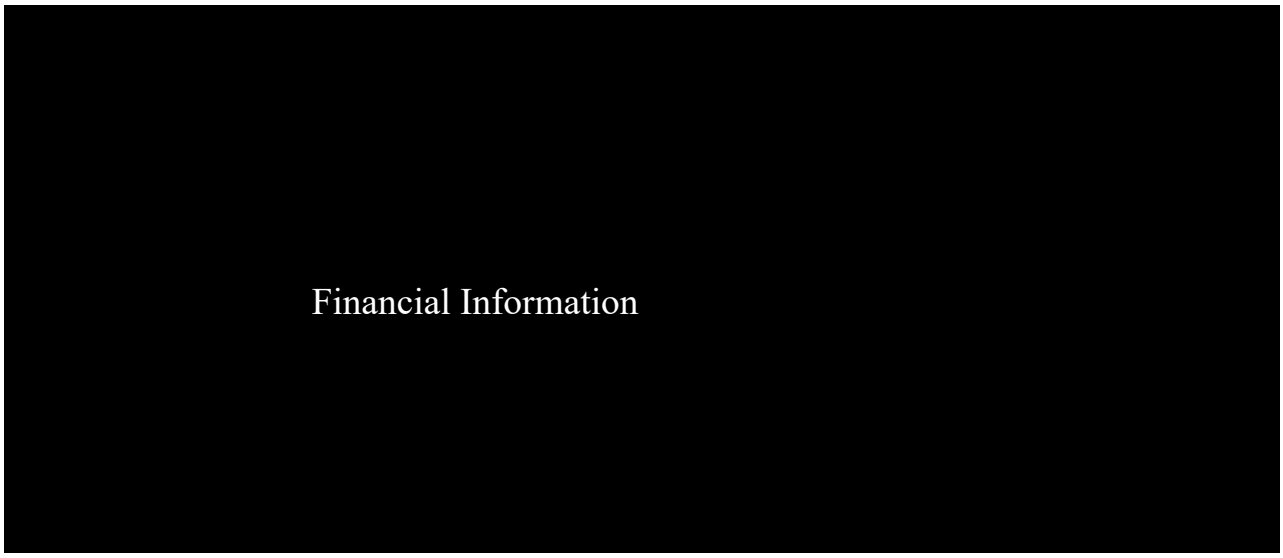
2. Consideration of Present Potential Launches

37. As discussed in Section IV.A.2, as many as twenty generics could enter the marketplace upon issuance of the Federal Circuit mandate [redacted] Settlement Agreements, and many of those manufacturers have already attained final FDA approval for generic oral fingolimod products.[46] In my present analysis, I have seen no evidence to indicate that the price erosion likely to result from the likely launch of this large number of generics would be meaningfully less severe than that resulting from generic entry in 2019. [redacted] Financial Information. A July 2022 Novartis presentation analyzing the impact of loss of exclusivity on an analogous branded product (Tecfidera) shows generic price discounts of up to [redacted]% off branded WAC one year after launch with [redacted] or more generics on the market.[47] Percentage and Number

[45] *See id.*
[46] As noted above, I find it more likely that the settled generics would launch in the event HEC were permitted to launch and launched first.
[47] Exhibit 2 at 3. *See also* Exhibit 3 at 8.

Figure 1: Novartis Insights from Tecfidera Loss of Exclusivity

Source: Exhibit 2 at 3



38. [redacted]

Financial Information

[redacted].[49]

39. Further, as discussed in Section IV.B, since 2019 the RRMS marketplace has become increasingly crowded. There have been additional launches of competing S1P modulators, including Mayzent, Zeposia and Ponvory, launches in other RRMS therapy classes, such as Kesimpta, Avonex and Extavia, and the

[48] Exhibit 2 at 3. *See also* Exhibit 3 at 16.
[49] Exhibit 2 at 3. *See also* Exhibit 3 at 8.

launch of generic Tecfidera offerings. Such an extensive breadth of current options has two key effects on the present irreparable harm analysis:

1) the incremental options relative to 2019 would afford payers additional bargaining power and enable them to extract larger price concessions from Novartis – making it even less plausible that Novartis would be able to restore its pre-generic pricing upon an eventual generic withdrawal;
2) the rapid proliferation of competing RRMS therapies demonstrates the inherent difficulty in quantifying any harm stemming from price erosion, even during the pendency of a generic launch. That is, forecasting the "but-for" sales volumes and pricing for branded Gilenya – a necessary input into a damages exercise to assess "but-for" conditions that would have existed during the pendency of the generic launch – in this increasingly dynamic marketplace is more difficult than it would have been in 2019 (when it already presented a considerable challenge).

40. Accordingly, I find that, as in 2019, current marketplace dynamics, specific aspects of Gilenya contracting practices, and the increasing asymmetry in bargaining power between Novartis and payers regarding RRMS therapies are all likely to result in significant and long-lasting price erosion in the oral fingolimod marketplace. Those factors will continue to substantially depress branded Gilenya pricing even following a potential generic withdrawal. Any past price erosion harm will be difficult to fully quantify and future harm from continued depressed prices will necessarily persist beyond the period of interim generic availability.

B. First Dose Observation Support Cessation and Corresponding Oral Fingolimod Volume Losses

1. Prior Analysis

41. In my 2019 analysis, I concluded that in addition to traditional share loss likely to be incurred by branded Gilenya as a result of the potential generic launches, the FDO requirements associated with oral fingolimod therapy represented an additional and significant threat to aggregate oral fingolimod prescription volumes. Unlike other RRMS therapies, Gilenya requires patients undertake FDO prior to initiating therapy, both for the first time and for any subsequent therapy initiation following a pause of 14 days or more.[50]

42. Novartis is well-aware that the FDO requirements represent a barrier to patients starting Gilenya therapy and has historically provided extensive patient support services to simplify Gilenya onboarding and adherence. Through the Gilenya Go Program, Novartis provides patients with assistance in scheduling, coordinating, and paying for the initial tests required to commence Gilenya therapy, like FDO, at significant cost to the company.[51]

43. I previously explained that following a generic launch, Novartis anticipated needing to significantly scale back all patient support programs, including its FDO services. I further explained that Novartis did not expect any

[50] *See* Vellturo PI Declaration, ¶¶ 81-84.
[51] *See id.*

generic manufacturers to provide FDO support themselves. Moreover, even to the extent that any third party (such as a payer) sought to establish their own patient support services following the cessation of the existing Novartis programs, any such effort would require a significant amount of time and would not be fully established until months after any at-risk launch.[52]

44. [redacted] Business Plans [redacted].[54]

45. I thus concluded that the overall marketplace share of oral fingolimod could shrink in favor of competitor treatments that are perceived as easier to use, and that Gilenya would be unlikely to regain the lost share (of oral fingolimod relative to other RRMS therapies) following generic withdrawal. Moreover, I noted that estimating the magnitude of such an effect would have been, based on my experience in assessing such issues, extremely difficult.

[52] *See id.*, ¶¶ 82-90.
[53] *See id.*, ¶¶ 91-95.
[54] *See id.*, ¶¶ 94-97.

2. Consideration of Present Potential Launches

46. Since undertaking my initial analysis in 2019, Novartis's planning for its patient services in light of a generic launch has not substantially changed. [redacted]

[redacted]

Business Plans

[redacted][57]

47. Relative to 2019, I would expect that the proliferation of additional RRMS therapies without FDO requirements, including generic Tecfidera products, Janssen's Ponvoy, and BMS's Zeposia, would in fact hasten the shift away from oral fingolimod in favor of other, less burdensome therapies following the cessation of patient support services.[58]

48. Thus, I find that a lack of support for the FDO process is, if anything, even more likely lead to aggregate oral fingolimod prescription attrition in the form

[55] Exhibit 1 at 2.
[56] *Id.,* at 7; Conversation with Joseph Gialanella and Cristian Azcarate.
[57] Conversation with Joseph Gialanella and Cristian Azcarate.
[58] I understand that this coincides with the expectations of Novartis personnel as well. Conversation with Joseph Gialanella and Cristian Azcarate.

of a limited ability to both initiate new patients and retain existing Gilenya patients who pause treatment.

C. Loss of Goodwill and Relationships

1. Prior Analysis

49. As discussed in my 2019 analysis, goodwill and positive relationships with other members of the medical community are key contributors to a pharmaceutical company's long-term success. Novartis currently benefits from enhanced goodwill in the medical community specifically stemming from the success of Gilenya. This is particularly true within the neuroscience community.

50. I concluded that the at-risk launch of generic oral fingolimod products would have diminished the brand recognition associated with Novartis and Gilenya, particularly given the likely decrease in overall fingolimod prescriptions due to the cessation of patient support services (as discussed in Section V.B). Further, that disruption of services may well have itself damaged Novartis's reputation in the medical space, jeopardizing the success of any future Novartis MS therapies and generating significant and long-lasting harm.

51. In addition to a potential loss of goodwill in the medical community at large, I explained that potential harm to Novartis's relationships with payers stemming from any attempt by Novartis to reinstate initial branded pricing following a generic withdrawal could have been particularly harmful. I concluded that

damaged relationships with payers could have complicated future contract negotiations relating to a number of Novartis therapies, leading Novartis to suffer additional long-lasting and difficult to quantify harm.

2. Consideration of Present Potential Launches

52. Since my 2019 analysis, nothing in the pharmaceutical marketplace has meaningfully changed such that I would expect any difference in the loss of goodwill associated with the cessation of Novartis's patient support programs and any attempts by Novartis to reinstate pre-generic pricing following generic withdrawal.[59]

VI. HARM TO HEC

53. As explained in my 2019 preliminary injunction declaration, the magnitude of harm that would have been sustained by defendants (including HEC) had a preliminary injunction been granted and subsequently withdrawn would have been significantly outweighed by the harm likely to be suffered by Novartis were the generic products allowed to launch.[60]

54. There have been no changes in the years since 2019 that change my opinion as to the magnitude of harm Novartis is likely to sustain relative to HEC and other generic entrants. As discussed in Section V.A, harm to Novartis will stem not only from lost unit sales but from the significant price erosion likely to occur on any

[59] Conversation with Joseph Gialanella and Cristian Azcarate.
[60] Vellturo PI Declaration, § V.

retained unit sales due to competition with generic entrants. As a result of this expected price erosion, harm to Novartis would necessarily be far greater than the harm potential generic entrants (including HEC) may face during the period between their launch and mid-2023.

55. I also understand that Novartis is willing to post a bond to compensate HEC for any harm that HEC suffers during the period of the stay, in the event the Supreme Court does not reverse. I note that HEC accepted, and Novartis posted, a preliminary injunction bond for the same purpose in the litigation before the District Court. It is my opinion that a bond would adequately protect HEC now for the same reason as it did in connection with the preliminary injunction.

VII. CONSIDERATION OF PUBLIC INTEREST

56. [redacted]

[redacted] Business Plans [redacted] Accordingly, patients seeking to begin RRMS treatment with fingolimod will be significantly less able to readily access services intended to facilitate the onboarding process. Indeed, as explained in my 2019 analysis, the generic manufacturers were not expected to provide any onboarding

services to prospective fingolimod patients themselves at that time,[61] and I understand that Novartis's expectations have not changed.[62] Economic logic supports this notion; there is no reasonable basis to conclude that generic manufacturers facing intense price competition and, accordingly, narrow profit margins, would have any incentive to provide such services.

57. [redacted]

Financial Information

[redacted]

[61] *Id.*, ¶ 87.
[62] Conversation with Joseph Gialanella and Cristian Azcarate.
[63] Conversation with Joseph Gialanella and Cristian Azcarate.

I declare under penalty of perjury that the foregoing is, to the best of my knowledge, true and correct.

Dated: September 23, 2022

Christopher Vellturo, Ph.D.

APPENDIX 1

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President

Over the course of his career, Dr. Vellturo has performed a wide variety of economic and econometric analyses and provided expert testimony in the context of mergers and acquisitions, antitrust litigation, intellectual property litigation and numerous other matters spanning a broad array of industries. Dr. Vellturo has testified on economics-related matters in numerous U.S. District Courts, as well as at the Canadian Competition Bureau, and before arbitral tribunals acting under the rules of arbitration of the American Arbitration Association. He has appeared before the U.S. Department of Justice, the Federal Trade Commission, various states' Attorneys General offices, the Federal Reserve Bank Board of Governors, and numerous other regulatory agencies on merger-related issues and other antitrust matters. Dr. Vellturo has also made appearances at hearings before the European Commission, and other antitrust enforcement agencies around the world. To date, he has performed economic analyses in over one hundred merger matters, in excess of seventy antitrust actions and well over one hundred intellectual property actions.

Dr. Vellturo has taught graduate-level economics at Boston University's School of Management.

Prior to forming Quantitative Economic Solutions, LLC (QES), Dr. Vellturo was a Principal at Analysis Group/Economics (AG/E) and a Senior Vice President and member of the Board of Directors at National Economic Research Associates (NERA).

Dr. Vellturo has published on a variety of topics, including merger and acquisition-related efficiencies, price discrimination, differentiated product analysis and market definition. His research has appeared in leading academic journals, including *Antitrust*, the *Antitrust Law Journal*, and the *Journal of Economics and Management Strategy*. Dr. Vellturo is a recipient of the Bradley Fellowship in Public Economics and has served as a referee for *American Economic Review* and *Rand Journal of Economics*.

A Ph.D. graduate in Economics from the Massachusetts Institute of Technology, Dr. Vellturo also holds a Sc.B. in Applied Mathematics and Economics from Brown University, where he graduated *magna cum laude* and *Phi Beta Kappa*.

EDUCATION

1989 Ph.D. in Economics, Massachusetts Institute of Technology
Primary Fields: Econometrics, Industrial Organization
Secondary Fields: Public Finance, Game Theory, Law and Economics

1983 Sc.B. in Applied Mathematics and Economics (*magna cum laude*), Brown University

PROFESSIONAL EXPERIENCE

2002-Present **Quantitative Economic Solutions, LLC**
President/Manager – Direct research on microeconomic issues in litigation and non-litigation matters. Areas of particular focus include: antitrust, regulation, and damages assessment in intellectual property and contract matters.

2008-2015 **Boston University, School of Management**
Instructor – Department of Finance & Economics

2000-2002 **Analysis Group/Economics**
Principal - Direct research and provide expert testimony on a variety of microeconomic issues with particular emphasis on antitrust, intellectual property, and mergers and acquisitions. Expert reports and testimony presented in U.S. District Court. Presented antitrust economic analyses to Federal Trade Commission, U.S. Department of Justice, Federal Reserve Bank Board of Governors and the European Commission.

1996-2000 **National Economic Research Associates, Inc.**
Senior Vice President (1999-2000)
Vice President (1996-1999)

1991-1996 **Cambridge Economics, Inc.**
Director - Directed research and provided expert testimony on a variety of microeconomic issues with particular emphasis on antitrust, intellectual property, and mergers and acquisitions. Prior expert testimony provided in U.S. District Court and before the American Arbitration Association. Presented antitrust economic analyses to U.S. Department of Justice, Federal Trade Commission (Antitrust Division), state Attorneys General offices, and the Federal Reserve Bank Board of Governors.

1989-1991 **National Economic Research Associates, Inc.**
Senior Consultant - Directed and performed research relating to issues of antitrust, intellectual property, mergers and regulation.

1987 **Department of Economics, M.I.T.**
Teaching Assistant - Undergraduate econometrics.

1985-1989 **Dean Ann F. Friedlaender, M.I.T.**
Research Associate - Participated in research relating to transportation pricing and capital allocation responses to regulatory changes.

1983-1985 **National Economic Research Associates, Inc.**
Research Associate - Conducted research on a wide variety of issues including antitrust, railroad rate setting, optimal landfill pricing, and PCB and asbestos abatement strategies.

AWARDS AND PROFESSIONAL ACTIVITIES

1987-1989	Recipient, Bradley Fellowship in Public Economics
1986	M.I.T. Departmental Fellowship
1983	Phi Beta Kappa, Brown University
1983	Sigma Xi, Brown University
Present	Journal Referee for *American Economic Review* and *Rand Journal of Economics*
Present	Member, American Economic Association
Present	Member, American Bar Association

TESTIFYING HISTORY (PAST FOUR YEARS)

- *United Services Automobile Association v. PNC Bank, N.A.*
  United States District Court for the Eastern District of Texas Marshall Division, Case No. 2:21-cv-0246-JRG

- *Advantest America, Inc.; and Advantest Test Solutions, Inc. v. Samer Kabbani; Lattice Innovation, Inc.; AEM Holdings LTD; and Wavem US Inc.*
  Before the JAMS Arbitration Panel, Reference No: 1200057839

- *Boston Scientific Corp. and Boston Scientific Neuromodulation Corp. v. Nevro Corp.*
  United States District Court for the District of Delaware, C.A. No. 16-1163 (CFC)

- *Astellas US LLC; Astellas Pharma US, Inc.; and Gilead Sciences Inc. v. Hospira, Inc.*
  United States District Court for the District of Delaware, C.A. No. 18-1675-CFC-CJB (Consolidated)

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  United States District Court for the Eastern District of Texas Marshall Division, Case No. 2:20-cv-00319-JRG

- *Anthony Colucci, Vanessa Lorraine Skipper, Individually and on Behalf of Those Similarly Situated v. Health First, Inc.*
  United States District Court for the Middle District of Florida, C.A. No. 6:21-cv-00681-RBD-GJK

- *I-Mab v. Tracon Pharmaceuticals, Inc.*
  ICC Case No. 25372/MK

- *Colibri Heart Valve LLC v. Medtronic CoreValve LLC*
  United States District Court for the District of California Southern Division, C.A. No. 8:20-cv-00847 (DOC) (JDE)

- *Teva Pharmaceuticals International GmbH v. Eli Lilly and Company*
  United States District Court for the District of Massachusetts, C.A. No. 1:18-cv-12029-ADB

- *Novo Nordisk Inc. and Novo Nordisk A/S v. Sandoz Inc.*
  United States District Court for the District of Delaware, C.A. No. 20-00747-CFC

- *Indivior Inc. and Indivior UK Limited v. Dr. Reddy's Laboratories S.A. and Dr. Reddy's Laboratories, Inc.*
  United States District Court for the District of New Jersey, Civil Action No. 17-07111-KM-CLW
  Indivior Inc., Indivior UK Limited and Aquestive Therapeutics, Inc. v. Alvogen Pine Brook LLC
  United States District Court for the District of New Jersey, Civil Action Nos. 17-cv-07106 (KM) (CLW), 18-5285-KM-CLW

- *Amgen Inc. et al. v. Sandoz Inc., et al.*
  United States District Court for the District of New Jersey, Civil Action No. 18-11026 (MAS)(DEA)

- *Plastipak Packaging, Inc. v. Premium Waters Inc.*
  United States District Court for the Western District of Wisconsin (Madison), Civil Action No. 3:20-cv-00098

- *Boehringer Ingelheim Pharmaceuticals Inc., et al. v. Mankind Pharma LTD., et al.*
  United States District Court for the District of Delaware, CA. No. 1:18-cv-01689-CFC (Consolidated)

- *AMO Development, LLC, AMO Manufacturing USA, LLC and AMO Sales and Service, Inc. v. Alcon LenSx, Inc., Alcon Vision, LLC, Alcon Laboratories, Inc. and Alcon Research, LLC.; Alcon Inc., Alcon LenSx, Inc., Alcon Research, LLC, and Alcon Vision, LLC. v. AMO Development, LLC, AMO Manufacturing USA, LLC, AMO Sales and Service, Inc., and Johnson and Johnson Surgical Vision, Inc.*
  United States District Court for the District of Delaware, C.A. No. 20-842 (CFC)

- *Novo Nordisk Inc. and Novo Nordisk A/S v. Mylan Institutional LLC*
  United States District Court for the District of Delaware, C.A. No. 19-01551-CFC

- *The Trustees of the University of Pennsylvania v. Eli Lilly and Company, ImClone LLC, and Bristol-Myers Squibb Company*
  United States District Court for the Eastern District of Pennsylvania, Case No. 2:15-cv-06133-PD

- *In the Matter of an Arbitration Under the CPR Non-Administered Arbitration Rules Between Ford Motor Company, on behalf of itself, its wholly and majority-owned subsidiaries, v. Ibiden Company, LTD., and all its direct and indirect subsidiaries.*

- *H. Lundbeck A/S; Takeda Pharmaceutical Company LTD.; Takeda Pharmaceuticals U.S.A., Inc; Takeda Pharmaceuticals International AG; and Takeda Pharmaceuticals America, Inc. v. Apotex, Inc., et al.*
  United States District Court for the District of Delaware, C.A. No. 18-88 (LPS) (Consolidated)

- *ViiV Healthcare Company, Shionogi & Co., Ltd. and ViiV Healthcare UK (No. 3) Limited v. Gilead Sciences, Inc.*
  United States District Court for the District of Delaware, C.A. No. 18-224-CFC-CJB

- *Ferring B.V., Ferring International Center S.A., and Ferring Pharmaceuticals, Inc. v. Serenity Pharmaceuticals, LLC and Reprise Biopharmaceuticals, LLC*
  United States District Court for the Southern District of New York, Case No. 17-cv-9922 (RWS) ECF CASE

- *OJ Commerce LLC; and Naomi Home, Inc. v. KidKraft, LP; and MidOcean Partners, LP.*
  United States District Court for the Southern District of Florida, Case No. 19-CV-60341-CIV-Cooke/Hunt

- *SAS Institute Inc. v. World Programming Limited; Luminex Software, Inc.; Yum! Brands, Inc.; Pizza Hut, Inc.; and Shaw Industries Group, Inc.*
  United States District Court for the Eastern District of Texas Marshall Division, Civil Action No. 2:18-CV-00295-JRG

- *Pfizer Inc., et al. v. Zydus Pharmaceuticals (USA), et al.*
  United States District Court for the District of Delaware, C.A. No. 17-158 (LPS)

- *Abbott Cardiovascular Systems, Inc., and Evalve, Inc. v. Edwards Lifesciences, LLC, and Edwards Lifesciences, Corp.*
  United States District Court for the District of Delaware, Case No. 1:19-cv-00149-MN

- *3M Company & 3M Innovative Properties Company v. Kerr Corporation*
  United States District Court for the District of Delaware, C.A. No. 17-01730-LPS-CJB

- *CardioNet LLC. and Braemar Manufacturing, LLC v. InfoBionic, Inc.*
  United States District Court for the District of Massachusetts, Civil Action No. 1:15-cv-11803-IT

- *Novartis Pharmaceuticals Corporation v. Accord Healthcare, Inc., et al.*
  United States District Court for the District of Delaware, C.A. No. 18-1043-LPS

- *Array Technologies, Inc. v. Colin Mitchell, NEXTracker, Marco Garcia, Daniel S. Shugar, Scott Graybeal, and Flextronics International U.S.A., Inc.*
  United States District Court for the District of New Mexico, Civil Action No. 1:17-cv-00087-JAP-LF

- *In the matter of the arbitration between Intellia Therapeutics, Inc. and Caribou Biosciences, Inc.*
  Before the JAMS Arbitration Panel, Reference No.: 1425027888

- *Astellas Pharma Inc., Astellas Ireland Co., Ltd., and Astellas Pharma Global Development, Inc. v. Actavis Elizabeth LLC, et al.*
  United States District Court for the District of Delaware, C.A. No. 1:16-905 (JFB0 (CJB) (Consolidated)

- *Orexo AB and Orexo US, Inc. v. Actavis Elizabeth, LLC, Actavis Pharma, Inc., Teva Pharmaceuticals USA, Inc., and Teva Pharmaceuticals Industries, Ltd.*
  United States District Court for the District of Delaware, C.A. No. 17-205-CFC

- *Adocia S.A. v. Eli Lilly and Company*
  The American Arbitration Association, AAA Case No. 01-17-0005-2264

- *RELX Inc. v. Informatica Corp.*
  United States District Court for the Southern District of New York, Case No. 16-cv-9718

- *Novo Nordisk Inc. and Novo Nordisk A/S v. Teva Pharmaceuticals USA, Inc.*
  United States District Court for the District of Delaware, C.A. No. 1:17-cv-00227

- *Zimmer Surgical, Inc. and Dornoch Medical Systems, Inc. v. Stryker Corporation and Stryker Sales Corporation; Stryker Corporation and Stryker Sales Corporation v. Zimmer Surgical, Inc., Zimmer, Inc. and Dornoch Medical Systems, Inc.*
  United States District Court for the District of Delaware, C.A. No. 16-679-RGA

- *Immunex Corporation, Amgen Manufacturing, Limited and Hoffman La-Roche Inc. v. Sandoz Inc., Sandoz International GMBH and Sandoz GMBH*
  United States District Court for the District of New Jersey, Civil Action No. 2:16-cv-01118

PUBLICATIONS AND PRESENTATIONS

"Trade Secrets Damages: Dangerous Waters." Presented at the Practicing Law Institute (PLI) Conference, Trade Secrets 2017: What every Lawyer Should Know, October 27, 2017.

"Lunch at Texas Law with Panel of Damages Experts." Presented at the University of Texas School of Law's Patent Damages Conference, Austin, Texas, June 9, 2016.

"Mock Trial: *Carnival Comics, Inc. v. DigiCom, LLP, et al.*" Presented at the 61st Annual Spring Meeting of the ABA Section of Antitrust Law, Washington, DC, April 11, 2013.

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July 2020

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

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Case Number: 21-1070

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

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