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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

APOTEX INC. AND
APOTEX CORP.
Petitioners,

v.

NOVARTIS A.G.,
Patent Owner.

IPR2017-00854
Patent No. 9,187,405

PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 9,187,405

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I. INTRODUCTION

Pursuant to 35 U.S.C. § 311 and § 6 of the America Invents Act ("AIA"), and 37 C.F.R. Part 42, Apotex, Inc. and Apotex Corp., ("Petitioners") request review of U.S. Patent No. 9,187,405 to Peter C. Hiestand *et al.* ("the '405 patent," EX1001) that issued on November 17, 2015, and is assigned to Novartis A.G. ("Patent Owner").

The '405 patent claims a method of administering fingolimod hydrochloride ("FTY720"), a previously known immunosuppressant, for the treatment of a subject with Relapsing-Remitting Multiple Sclerosis ("RR-MS"). The claimed method recites "a daily dosage of 0.5 mg" that was known and reported to be safe and pharmacologically effective in humans more than one year before the earliest effective filing date of the '405 patent. For example, International Publication No. WO 2006/058316 ("Kovarik," EX1004), teaches treating multiple sclerosis by administering a 0.5 mg oral daily dose of fingolimod hydrochloride.

The '405 patent claims also employ a negative limitation regarding the absence of a loading dose regimen. Yet, Kovarik teaches that a maintenance dose is a therapeutically effective dose and teaches 0.5 mg fingolimod hydrochloride as a standard daily (maintenance) dose for treating MS. Indeed, the evidence shows that of the six FDA-approved treatments for RR-MS, none described the use of loading doses as part of an approved regimen.

The prior art also teaches 0.5 mg fingolimod hydrochloride was pharmacologically effective in inducing lymphopenia (the mechanism by which fingolimod hydrochloride was understood to treat MS). Moreover, the prior art teaches that fingolimod hydrochloride was effective in treating RR-MS by reducing, preventing or alleviating relapses and slowing the progression of the disease. In view of the prior art, it would have been obvious to administer a 0.5 mg daily dose of fingolimod hydrochloride absent an immediately preceding loading dose regimen to a patient with RR-MS.

This petition also establishes that the negative limitation regarding the absence of a loading dose regimen was not supported by the ’405 patent specification, nor in any priority documents. Thus, claims 1-6 of the ’405 patent are anticipated by the 2010 disclosure of the results of a phase III clinical trial administering a 0.5 mg daily dose of fingolimod hydrochloride for the treatment of RR-MS.

For the reasons discussed herein, this Petition demonstrates by a preponderance of the evidence that it is more likely than not that claims 1-6 of the ’405 patent are unpatentable for failing to distinguish over prior art and should be found unpatentable and canceled.

A. Brief Overview of the ’405 Patent

The ’405 patent is entitled “S1P Receptor Modulators for Treating

Relapsing-Remitting Multiple Sclerosis." In a general sense, the '405 patent is directed to the use of sphingosine 1-phosphate (S1P) receptor agonists for the treatment of demyelinating diseases such as multiple sclerosis. *See, e.g.*, EX1001, 1:5-8; EX1002, ¶13. The specification describes a genus of sphingosine analogs (*id.* at 1:15-18), including 2-amino-2-[2-(4-octylphenyl)ethyl]propane-l,3-diol hydrochloride, also known as fingolimod hydrochloride or as FTY720. *Id.* at 8:18-30; EX1002, ¶¶8, 12, 16, 56.

The '405 patent asserts that S1P agonists "are known as having immunosuppressive properties or anti-angiogenic properties," and that "multiple sclerosis (MS) is an immune-mediated disease of the central nervous systems[.]" EX1001, 8:56-67. No data on the efficacy of the claimed method to treat or slow the progression of RR-MS are presented in the '405 patent. EX1002, ¶¶15-16. The patent also does not present data on the effect of the claimed method on relapse reduction, prevention, or alleviation in patients suffering from RR-MS. *Id.* Instead, prophetically-written experiments are described to permit an assessment of whether compounds such as fingolimod hydrochloride are able to "completely inhibit[] the relapse phases" using a rat model of relapsing multiple sclerosis. EX1001, 10:67; *see also id.* at 10:32-11:2. A clinical trial is also proposed to assess the claimed methods' "clinical benefit" in RR-MS patients. EX1001, 11:6-38. EX1002, ¶16.

Claim 1 of the ’405 patent is representative of the independent claims at issue:

> 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.

EX1001, 12:49-55; EX1002, ¶9. Independent claims 3 and 5 are also directed to administering a daily oral 0.5 mg dose of fingolimod, in free form or as a salt, to a subject in need, absent an immediately preceding loading dose regimen. EX1001, 12:59-13:6; EX1002, ¶¶10-11. Claim 3 specifies that the subject is in need of a method for treating RR-MS. EX1001, 12:59-13:6. Claim 5 specifies that the subject is in need of a method for slowing progression of RR-MS. *Id.* Claims 2, 4, and 6 depend, respectively, from claims 1, 3, and 5, and each specify that fingolimod is administered as fingolimod hydrochloride. *Id.* at 12:56-13:9; EX1002, ¶12.

B. Brief Overview of the Prosecution History

The patent application that matured into the ’405 patent, 14/257,342 (“the ’342 application”), was filed on April 21, 2014, as a divisional application of 13/149,468 (“the ’468 application”), which itself issued as U.S. Patent No.

8,741,963 ("the '963 patent," EX1013). EX1002, ¶¶17-19, 22. The '468 application was filed as a continuation of 12/303,765 ("the '765 application," EX1009), which was the U.S. entry of PCT/EP2007/005597 that was filed on June 25, 2007. *Id.* PCT/EP2007/005597 claims priority to foreign application GB0612721.1 (EX1012), which was filed on June 27, 2006. EX1001 at cover.

The claims of the '342 application were initially rejected as obvious over Virley, *Developing Therapeutics for the Treatment of Multiple Sclerosis*, NEURORX, 2:638-649 (2005) ("Virely," EX1016) and International Publication No. WO 2006/058316 (published June 1, 2006) ("Kovarik," EX1004). EX1011 at 0052-56; EX1002, ¶¶23-24. Patent Owner offered only attorney argument in response to the non-final rejection. EX1011 at 0033-34; EX1002, ¶25. A notice of allowance ensued. EX1011 at 0007; EX1002, ¶26.

C. Brief Overview of the Grounds

Ground 1 provides new evidence and argument regarding the obviousness of the challenged claims in view of Kovarik (EX1004) and Thomson (EX1005), with only the former reference having been discussed substantively during prosecution. For example, this petition is accompanied by the supporting declaration of Dr. Barbara S. Giesser, Professor of Clinical Neurology at UCLA with over 30 years of experience in the treatment of patients with, and research regarding, multiple sclerosis. EX1002, ¶¶1-4. Dr. Giesser states that, in her opinion, several of the

assertions made by the Applicants' attorneys during prosecution to overcome the rejection are incorrect. EX1002, ¶27.

For one, Dr. Giesser notes that the Applicants' attorneys argued that the maintenance dose is "dependent on the immediately preceding loading dose," thereby incorrectly implying that the maintenance dose disclosed for the treatment of MS in Kovarik would be inapplicable absent an immediately preceding loading dose. EX1011 at 0033; EX1002, ¶28. As explained by Dr. Giesser, however, therapeutic efficacy of a maintenance dose depends on the desired steady-state plasma concentration and the clearance rate of the drug, neither of which are dependent on a loading dose regimen. EX1002, ¶¶29-30, citing EX1021 at 91, 93 (which teaches that a "maintenance dose…is equal to the product of clearance…and [the] desired steady state plasma concentration.…"). A loading dose regimen merely increases the speed at which this steady-state plasma concentration is achieved. *Id.*; EX1002, ¶¶19-20, 57. Thus, Applicants' attorney argument that daily dosage depends on a given loading dose regimen is contradicted by the teachings of Kovarik and the expert testimony of Dr. Giesser.

Applicants' attorneys further argued that a skilled artisan "would attach no significance to the suitability of any daily dosage mentioned therein [Kovarik] outside the context of an immediately preceding loading dose regimen." EX1011 at

0034; EX1002, ¶¶29-30. Dr. Giesser notes this unsupported assertion is contradicted by Kovarik itself, which teaches:

> Preferred medications comprise medication for . . . patients suffering from autoimmune diseases, e.g., multiple sclerosis. . . . In view of the normally prolonged taking of the medication, ***the standard daily dosage (also called maintenance dose) refers to the dosage*** of an S1P receptor modulator or agonist ***necessary for*** a steady-state trough blood level of the medication or its active metabolite(s) ***providing effective treatment***.

EX1004 at 14 (emphasis added). Thus, Kovarik confirms that the 0.5 mg maintenance dose is effective for the treatment of multiple sclerosis regardless of whether it was immediately preceded by a loading dose regimen. EX1002, ¶¶29-30; *see also* EX1010 at 0109 ("standard daily dosage" is "the dosage necessary for a steady-state trough blood level of the drug providing effective treatment.").

The Applicants' attorneys also argued that the "daily dosage administered after the initial period can vary substantially relative to the standard daily dosage." EX1011 at 0033. However, as Dr. Giesser notes, Kovarik teaches administering fingolimod hydrochloride in the narrow range of 0.1 mg - 0.5 mg per day in the treatment of autoimmune diseases, including multiple sclerosis. EX1004 at 17; EX1002, ¶27. She also notes that Kovarik teaches a dosing regimen that involves maintenance therapy with a 0.5 mg daily dose. EX1004 at 15; EX1002, ¶76. Thus,

Kovarik not only teaches a narrow range of maintenance doses for MS treatment that encompasses the Applicants' claimed daily dose, but also specifically describes the claimed 0.5 mg daily dosage as part of a preferred embodiment. EX1004 at 15 ("[T]reatment is continued with the maintenance therapy, e.g. a daily dosage of 0,5 mg.").

For the reasons discussed above, the Board should not defer to the Patent Owner's unsupported attorney arguments during prosecution.

Ground 2 presents new arguments and evidence regarding the obviousness of the challenged claims in view of Chiba (EX1006), Kappos 2005 (EX1007), and Budde (EX1008). Chiba was not of record during prosecution of the '405 patent. Kappos 2005 and Budde were not substantively discussed during prosecution.

Ground 3 presents new arguments and evidence regarding the unpatentability of the challenged claims in view of Kappos 2010 (EX1038), which was not of record during prosecution of the '405 patent. Ground 3 presents an argument not previously considered by the Patent Office that the claims of the '405 patent are not entitled to the benefit of a filing date earlier than April 21, 2014.

For the reasons discussed above, the Board should consider the evidence and arguments in this petition without substantial deference to the decision by the Office to allow the '342 application.

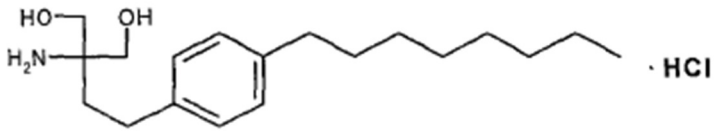
D. Brief Overview of the Scope and Content of the Prior Art

The priority document for the '405 patent is a foreign patent application (GB 0612721.1, EX1012), which was filed June 27, 2006. For the purposes of pre-AIA 35 U.S.C. § 102(b), the relevant date is that of first United States filing. *See* 35 U.S.C. § 119(a) (pre-AIA) ("[B]ut no patent shall be granted on any application for patent for an invention which had been patented or described in a printed publication in any country more than one year ***before the date of the actual filing of the application in this country***, or which had been in public use or on sale in this country more than one year prior to such filing."); *see also* MPEP § 706.02 ("In examining applications subject to pre-AIA 35 U.S.C. 102, the effective filing date is the filing date of the U.S. application… not the filing date of the foreign priority document."). In this case, "the actual filing of the application in this country" is no earlier than June 25, 2007, the filing date of PCT/EP2007/005597. Therefore, at least publications that pre-date June 25, 2006, are prior art to the claims of the '405 patent under 35 U.S.C. § 102(b).

i. International Publication No. WO 2006/058316 ("Kovarik," EX1004)

Kovarik is a PCT application that published in English on June 1, 2006, and was filed as PCT/US2005/043044 by Novartis Pharma GmbH on November 28, 2005. Kovarik claims priority to U.S. Provisional Application No. 60/631,483 (filed November 29, 2004) (EX1015). EX1002, ¶74.

Kovarik discloses a genus of agonists for the S1P receptor that are "useful for the treatment of inflammatory and autoimmune diseases" due to their "immune-modulating potency." EX1004 at 1; EX1002, ¶75. Kovarik teaches that "preferred" species are those "which in addition to their S1P binding properties also have accelerating lymphocyte homing properties, e.g. compounds which elicit a lymphopenia[.]" EX1004 at 2. Kovarik teaches "[a] particularly preferred S1P receptor agonist … 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 . . . e.g. the hydrochloride, as shown:



." *Id.* at 13; EX1002, ¶75.

Kovarik teaches daily oral dosage regimens of fingolimod hydrochloride (FTY720) for the treatment of "autoimmune diseases, e.g. multiple sclerosis," and for preventing organ rejection. EX1004 at 14, 18. Kovarik teaches "[a] method for treating an autoimmune disease in a subject in need thereof, comprising administering to the subject, after a loading regimen, a daily dosage of FTY720 of about 0.1 to 0.5mg." *Id.* at 17; EX1002, ¶¶76-77. Kovarik further teaches that the standard daily (maintenance) dosage of 0.5 mg FTY720 may be administered for the treatment of multiple sclerosis and that the loading dose regimen allows for a

steady-state concentration of FTY720 to be achieved in less than one week. EX1004 at 14-15, 17; EX1002, ¶¶77-78, 105.

Kovarik published on June 1, 2006, and is prior art to the claims of the '405 patent at least under 35 U.S.C. §§ 102(a), (b), (e).

ii. Thomson, *FTY720 in multiple sclerosis: the emerging evidence of its therapeutic value,* CORE EVIDENCE, 1(3): 157-167 (2006) ("Thomson," EX1005)

Thomson reviews medical literature describing the use of FTY720 in the treatment of multiple sclerosis. EX1005 at 157, EX1002, ¶81. Thomson teaches that FTY720 reduces inflammatory disease activity, thereby reducing relapse rates, increasing the time to first relapse, and increasing intervals between relapses:

> FTY720 (administered orally once a day for up to 12 months) improved the patient-oriented outcomes of relapse rate and the likelihood of remaining relapse-free. In addition, there is moderate evidence that disease-oriented outcomes were also improved by FTY720 in that inflammatory disease activity (both new and existing) was reduced as determined by MRI.

EX1005 at 166-67; EX1002, ¶¶83, 85-86. Thomson concludes, "FTY720 has the potential to be an effective disease-modifying agent for the treatment of RRMS." EX1005 at 167; EX1002, ¶82.

Thomson additionally provides data from clinical trials focused on the use of fingolimod hydrochloride in preventing organ rejection following transplantation.

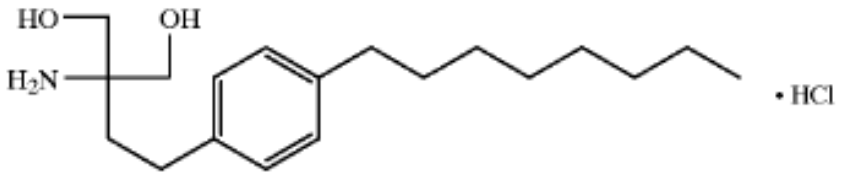
EX1005 at 157; EX1002, ¶84. Thomson explains that "[p]harmacokinetic and pharmacodynamic outcomes . . . are not affected by disease status and may be extrapolated to include those patients with multiple sclerosis." EX1005 at 162; EX1002, ¶84. Thomson additionally explains that induction of a reversible lymphopenia provides for "good evidence that FTY720 achieves immunomodulation" and thus "has the potential to be an effective disease modifying agent for the treatment of multiple sclerosis." EX1005 at 157; *see also* EX1002, ¶¶58, 60-61, 64, 84, citing EX1022 at 309, EX1018 at 237-39, Park, *et al.*, *Pharmacokinetic/Pharmacodynamic Relationships of FTY720 in Kidney Transplant Patients*, BRAZILIAN JOURNAL OF MEDICAL AND BIOLOGICAL RESEARCH, 38: 683-694 (2005) ("Park," EX1019) at 684, EX1031 at 1081, EX1028 at 440. Thomson teaches that single oral doses in the range of 0.25 to 3.5 mg are sufficient to induce lymphopenia and that there is "[n]o clear dose response" over this dose range. EX1005 at 163; EX1002, ¶85.

Thomson published on March 31, 2006 (*see also* EX1040) and is prior art to the claims of the '405 patent at least under 35 U.S.C. §§ 102 (a) and (b).

iii. U.S. Patent No. 6,004,565 to Chiba ("Chiba," EX1006)

Chiba teaches compounds that promote accelerated lymphocyte homing ("ALH"), "show superior immunosuppressive effects and are useful themselves, or in methods, for the prevention or treatment of . . . autoimmune diseases such as . . .

multiple sclerosis[.]" EX1006, 2:55-58; *id.* at 6:26-49; EX1002, ¶¶90-91. Chiba notes a preferred ALH-immunosuppressive compound called "FTY720, 2-amino-2[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride, shown below.



." EX1006, 4:64-5:7; EX1002, ¶90. Thus, Chiba teaches that FTY720, fingolimod hydrochloride, suppresses the immune response of mammals through accelerated lymphocyte homing and is useful for the treatment of MS. EX1006, 4:64-67; EX1002, ¶90. Chiba teaches oral administration of FTY720 in a 0.01-10 mg daily oral dose. EX1006, 6:26-31, 6:41-43, 8:19-34, 11:20-21; EX1002, ¶¶91-92.

The Board has previously considered Chiba as part of IPR2014-00784 – an *inter partes* review of U.S. Patent No. 8,324,283 ("the '283 patent," EX1037). The '283 patent, assigned to Novartis AG and Mitsubishi Pharma Corporation, claims pharmaceutical compositions of fingolimod. The Board outlined the teachings of Chiba in the Final Written Decision finding the claims of the '283 patent unpatentable:

> Chiba teaches immunosuppressive compounds with fingolimod as the preferred species. Chiba also teaches that the immunosuppressive compounds it teaches are useful for treating "transplantation rejection

> of organs or tissues" and "autoimmune diseases such as … multiple sclerosis," among other diseases and conditions. Chiba teaches oral administration of fingolimod[.]

IPR2014-00784, Paper 112, Final Written Decision ("the '784 decision," EX1032) at 10 (citations removed). On the record in that IPR, the panel stated, "Chiba itself suggested treating multiple sclerosis using a solid oral form of fingolimod." *Id.* at 25.

Chiba issued in 1999 and is prior art to the claims of the '405 patent at least under 35 U.S.C. §§ 102 (a) and 102(b).

iv. Kappos, *et al.*, *FTY720 in relapsing MS: results of a double-blind placebo-controlled trial with a novel oral immunomodulator*, JOURNAL OF NEUROLOGY 252(Suppl 2): 11/41, Abstract O141(2005) ("Kappos 2005," EX1007)

Kappos 2005 teaches that FTY720, fingolimod hydrochloride, "reversibly sequesters tissue damaging T and B cells away from blood and the central nervous system to peripheral lymph nodes." EX1007 at 41, abstract O141; EX1002, ¶94. Kappos 2005 teaches that "FTY720 has demonstrated both preventative and therapeutic efficacy" in several animal models of MS. EX1007 at 41, abstract O141; EX1002, ¶94.

Kappos 2005 discloses the results of a Phase II randomized, double-blind, placebo-controlled study sponsored by Novartis Pharma AG Basel. *Id.*; EX1002, ¶94. The trial evaluated the efficacy of daily oral doses of FTY720 for the

treatment of relapsing multiple sclerosis patients. EX1007 at 41, abstract O141; EX1002, ¶94. Kappos 2005 reports "demonstrated efficacy of FTY720 on MRI and relapse-related endpoints," including the total number and volume of lesions as evaluated in monthly post baseline MRI scans. EX1007 at 41, abstract O141; EX1002, ¶95. Kappos 2005 also reported that FTY720 provided a higher "proportion of relapse-free patients," as well as a lower "annualized relapse rate" and longer "time to first relapse" as compared to placebo. EX1007 at 41, abstract O141. Additionally, Kappos 2005 teaches that there were "no compelling dose-related difference in efficacy on MRI or clinical endpoints." *Id.* Kappos 2005 states that these results "strongly suggest that FTY720 has the potential to be an efficacious disease modifying treatment for relapsing forms of MS with the additional benefit of once daily oral administration." *Id.*; EX1002, ¶95.

Kappos 2005 published in 2005[1] and is prior art to the claims of the '405 patent at least under 35 U.S.C. §§ 102 (a) and 102 (b).

v. Budde, *et al.*, *First human trial of FTY720, a novel immunomodulator, in stable renal transplant patients*, JOURNAL

[1] Kappos 2005 is an abstract for an oral presentation presented between June 18-22, 2005 in Vienna, Austria, and was published in the second 2005 supplemental issue of the 252nd volume of the *Journal of Neurology.* Kappos 2005 is also cited in Thomson. EX1005 at 167.

OF THE AMERICAN SOCIETY FOR NEPHROLOGY, 13:1073-1083 (2002) ("Budde," EX1008)

Budde describes a clinical study of FTY720 in renal transplant patients. EX1008 at 1073; EX1002, ¶97. Budde teaches that oral doses of 0.25, 0.5, 0.75, 1, 2, and 3.5 mg are each effective for induction of lymphopenia within 4.7-8 hours of administration. EX1008 at 1078; EX1002, ¶97. Budde expressly teaches the safety and lymphopenia-inducing efficacy of administering a dose of 0.5 mg FTY720. EX1008 at 1075-76; EX1002, ¶98. Budde also teaches that at "doses ranging from 0.5 mg to 3.5 mg, no clear dose response relationship was detected[.]" *Id*. at 1079; EX1002, ¶98. However, Budde teaches that doses ≥0.75 mg are associated with bradycardia (slowing of the heart rate). EX1008 at 1075-76; EX1002, ¶98.

Budde was previously considered by a panel of the Board in IPR2014-00784. In ruling on the admissibility of expert testimony relying on Budde, the Board concluded:

> [T]he evidence of record shows that Budde describes a clinical effect of a low dose of fingolimod and that a formulator would attempt to use the proper effective dose when studying compatibility with excipients. ("Single oral doses of FTY720 ranging from 0.25 to 3.5 mg … caused a reversible selective lymphopenia.")[.]

EX1032 at 52. Budde was published in 2002 and is prior art to the claims of the '405 patent at least under 35 U.S.C. §§ 102 (a) and 102 (b).

vi. Kappos, *et al.*, *A Placebo-Controlled Trial of Oral Fingolimod in Relapsing Multiple Sclerosis*, NEW ENGLAND JOURNAL OF MEDICINE, 362(5):387-401 (2010) ("Kappos 2010," EX1038)

Kappos 2010 is prior art to the claims of the '405 patent at least under 35 U.S.C. §§ 102 (a) and 102 (b) because the claims of the '405 are not entitled to the benefit of any pre-2010 filing date. As issued, the claims recite that 0.5 mg fingolimod is administered "absent an immediately preceding loading dose regimen." EX1001, 12:49-13:9. This negative claim limitation first appeared in the '342 application in a preliminary amendment submitted August 18, 2014. EX1011 at 0079-81. The originally filed '342 application, the resulting '405 patent, and each of the priority documents on which the '342 relies, are otherwise silent on whether or not to use a loading dose regimen. EX1002, ¶¶15, 144; EX1011 at 0111-27; EX1012 (GB0612721.1); EX1009 (Appl. No. 12/303,765); EX1010 (Appl. No. 13/149,468). Although the negative limitation was also added to the claims in the related '468 application (EX1010 at 0085-86), this occurred after its 2011 filing date.

Because none of its priority documents provide any reason prior to at least 2011 to exclude a loading dose regimen, or even mention the presence or absence of a loading dose regimen, the '405 patent is therefore entitled to a priority date no earlier than the filing date of the '342 application, April 21, 2014, or the date of the preliminary amendment, August 18, 2014. *Santarus, Inc. v. Par Pharm., Inc.*, 694

F.3d 1344, 1351 (Fed. Cir. 2012) ("Negative claim limitations are adequately supported when the specification describes a reason to exclude the relevant limitation."); *In re Bimeda Research & Dev. Ltd.*, 724 F.3d 1320, 1323 (Fed. Cir. 2013) (Affirming lack of written description support for a negative claim limitation because the disclosure did not "describe[] a formulation excluding a specific species."). Thus, documents published at least before April 21, 2013, including Kappos 2010, are prior art to and may be applied against the claims of the '405 patent under 35 U.S.C. § 102(b).

Kappos 2010 discloses the results of a Phase III randomized, double-blind, placebo-controlled study sponsored by Novartis Pharma. EX1038 at 387; EX1002, ¶100. Daily oral doses of 0.5 mg FTY720, also known as fingolimod hydrochloride, were studied in RR-MS patients over a period of 24 months. EX1038 at 387; EX1002, ¶100. Kappos 2010 teaches that, as compared to placebo, daily oral doses of 0.5 mg FTY720 significantly reduced "[r]ates of relapse, progression of clinical disability, and MRI evidence of inflammatory lesion activity and tissue destruction[.]" EX1038 at 400; EX1002, ¶100.

E. Brief Overview of the Level of Skill in the Art

A person of ordinary skill in the art in the relevant field as of June 27, 2006 or April 21, 2014 would typically include a person with a medical degree (M.D.) and several years of experience treating multiple sclerosis patients. EX1002, ¶¶39-

40. Such a person would be familiar with administering therapeutic agents for the treatment of multiple sclerosis, including RR-MS, and dosing regimens of the various therapeutic agents available for treating RR-MS. *Id*. Further, such a person would be knowledgeable about the multiple sclerosis medical literature available at the relevant time. EX1002, ¶¶39-40.

As discussed above, this Petition is supported by the expert testimony of Barbara Giesser, M.D., an expert in the field of RR-MS treatment with more than 30 years of experience. EX1002, ¶¶1-4; EX1003 at 1. She has authored or co-authored numerous peer-reviewed journal articles, book chapters, abstracts and literature reviews. *Id.*; EX1003 at 8-14. She has been principal or co-investigator on grants from the National Multiple Sclerosis Society that focus on clinical evaluation and methods of treatment. EX1002, ¶4; EX1003 at 4-5. Dr. Giesser has been elected as a Fellow in the American Academy of Neurology and the American Neurological Association and has served also on the Board of Directors for the Southern California chapter of the National Multiple Sclerosis Society. EX1002, ¶3. A further discussion of her qualifications can be found in her declaration as well as in her CV (EX1003). Dr. Giesser is well qualified as an expert, possessing the necessary knowledge and experience about treating MS patients, an understanding of related the scientific literature, as well as expertise

necessary to determine and explain the level of ordinary skill in the art as of June 27, 2006 or April 21, 2014.

II. GROUNDS FOR STANDING

Petitioners certify that, under 37 C.F.R. § 42.104(a), the '405 patent is available for *inter partes* review, and Petitioners are not barred or estopped from requesting *inter partes* review of the '405 patent on the grounds identified.

III. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8

Real Parties-in-Interest (37 C.F.R. § 42.8(b)(1)): Petitioners Apotex, Inc., and Apotex Corp. are the real parties-in interst. Additional real parties-in-interest are Apotex Pharmaceuticals Holdings Inc. and Apotex Holdings, Inc.

Related Matters (37 C.F.R. § 42.8(b)(2)):

In IPR2014-00784, all claims of U.S. Patent No. 8,324,283 (EX1037), were found unpatentable as obvious on September 24, 2015. EX1032 (Final Written Decision, Paper 112). Although not from the same patent family as the '405 patent, the '283 patent included claims to pharmaceutical compositions of fingolimod, or a pharmaceutically acceptable salt thereof, that is suitable for oral adminstration, as well as claims directed to the treatment of multiple sclerosis using S1P receptor agonists.

Lead and Back-Up Counsel (37 C.F.R. § 42.8(b)(3))

Lead Counsel: Steven W. Parmelee (Reg. No. 31,990)

Back-Up Counsel: Michael T. Rosato (Reg. No. 52,182)

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Service Information – 37 C.F.R. § 42.8(b)(4). Petitioners hereby consent to electronic service.

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IV. STATEMENT OF THE PRECISE RELIEF REQUESTED

Petitioners request review of claims 1-6 of the '405 patent under 35 U.S.C. § 311 and AIA § 6, as follows:

Ground	Claims	Description
1	1-6	Obvious under § 103 over Kovarik in view of Thomson
2	1-6	Obvious under § 103 over Chiba in view of Kappos 2005 and Budde
3	1-6	Anticipated under § 102 by Kappos 2010

V. STATEMENT OF NON-REDUNDANCY

Each of the Grounds raised in this Petition is meaningfully distinct. Ground 1 asserts the obviousness of claims 1-6 based on the teachings of Kovarik in view of the teachings of Thomson. Kovarik teaches a daily maintenance dose of 0.5 mg

fingolimod, in free form or as its hydrochloride salt FTY720, to treat multiple sclerosis. Thomson teaches the administration of FTY720 to reduce relapses, slow progression, and treat RR-MS in RR-MS patients. Ground 2 asserts the obviousness of claims 1-6 based on the teachings of Chiba in view of the teachings of Kappos 2005 and Budde. Chiba teaches a daily dose of 0.01-10 mg FTY720 in the treatment of multiple sclerosis. Kappos 2005 teaches that fingolimod hydrochloride reduces relapses, slows progression, and treats RR-MS. Budde teaches that a single 0.5 mg dose of FTY720 is sufficient to induce lymphopenia (immunosuppression) in humans and that no clear dose response effect exists for doses between 0.5 and 3.5 mg.

Ground 3 asserts anticipation of claims 1-6 based on the disclosure of Kappos 2010 and asserts that the claims are not entitled to the benefit of a filing date earlier than April 21, 2014.

VI. CLAIM CONSTRUCTION

An unexpired claim subject to *inter partes* review receives the broadest reasonable construction in light of the specification of the patent. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee,* 136 S. Ct. 2131, 2142 (2016); EX1002, ¶41.

i. "a subject in need"

Each of the independent claims recites a method comprising daily oral

administration of 0.5 mg fingolimod absent an immediately preceding loading dose regimen to "a subject in need." Each claim further refers to "reducing or preventing or alleviating relapses," "treating," and "slowing progression" of RR-MS. EX1002, ¶¶43-45. Under the broadest reasonable construction, a subject with RR-MS is "a subject in need" of treating RR-MS, of reducing, preventing, or alleviating relapses, and of slowing progression of RR-MS *Id.* The '405 patent explains that RR-MS involves relapses, which it describes as "attacks that occur over 1-2 weeks and often resolve over 1-2 months." *Id.* at 9:66-10:1. It also explains that "[s]ome patients accrue disability with each episode[.]" *Id.* at 10:1-3; *see also* MCALIPINE'S MULTIPLE SCLEROSIS, 4th Edition, Compston, ed (Elsevier, Inc., December 2005) ("McAlpine," EX1023) at 193 (RR-MS patients accrue neurologic disability over time because of incomplete recovery from relapses). The '405 patent also explains that half of patients who "initially experience the RR form of MS . . . will develop the secondary progressive form" within 10 years. EX1001, col. 9, l. 64-col. 10, l. 5; *see also* EX1023 at 195. Thus, an RR-MS patient is in need of a treatment that reduces, prevents or alleviates relapses and slows the progression of RR-MS. Daily administration of 0.5 mg fingolimod hydrochloride to a subject with RR-MS absent an immediately preceding loading dose regimen therefore satisfies each of claims 1-6.

ii. "A method for…"

The phrase "A method for…" in the preambles of each of claims 1, 3, and 5 at most merely describes the intended purpose of the method and that the subject receiving the fingolimod is a subject with RR-MS. EX1002, ¶¶44-45. Other than identifying the subject as a subject with RR-MS, none of the preambles provide any structure to the claimed method, and they are not required to breathe life into the claim, were not used to distinguish over the prior art, and are non-limiting. *Bristol Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1375 (Fed. Cir. 2001) ("the method [is] performed in the same way regardless [of] whether or not the patient experiences" an efficacious result); *see also Catalina Mktg. Int'l v. Coolsavings.com, Inc.*, 289 F.3d 801, 809 (Fed. Cir. 2002) ("[P]reambles describing the use of an invention generally do not limit the claims…."); *Sanofi-Aventis U.S. LLC et al. v. Fresenius Kabi USA, LLC, et al.*, Case No. 14-7869, at 10-11 (D. Del. October 7, 2016) (inclusion in preamble of antecedent description of patient recited in body of the claim does not make the purpose described in the preamble limiting); *Aspex Eyewear, Inc. v. Marchon Eyewear, Inc.*, 672 F.3d 1335, 1347 (Fed. Cir. 2012) ("as a general rule preamble language is not treated as limiting."); *Braintree Labs., Inc. v. Novel Labs., Inc.,* 749 F.3d 1349, 1357 (Fed. Cir. 2014) (preamble "not limiting 'where a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose

or intended use for the invention,'" (quoting *Rowe v. Dror,* 112 F.3d 473, 478 (Fed. Cir. 1997))).

The claims do not require that these methods achieve any particular therapeutic outcome, and the specification acknowledges that MS therapy "is only partially effective[.]" EX1001, 8:64-67; EX1002, ¶¶45-47. Thus, under the broadest reasonable interpretation, the preambles do not limit the claims to require an actual reduction in relapses or an actual slowing of RR-MS progression, as opposed to merely a hope or intention that such an effect may result. *Id.*

VII. BACKGROUND KNOWLEDGE IN THE ART PRIOR TO JUNE 27, 2006

The following background publications document knowledge that skilled artisans would bring to bear in reading the prior art. *Ariosa Diagnostics v. Verinata Health, Inc.*, 805 F.3d 1359, 1365 (Fed. Cir. 2015). This knowledge assists in understanding why one of ordinary skill would have been motivated to combine or modify the references asserted in the grounds of this petition to arrive at the claimed invention. As *KSR* established, 550 U.S. 398, 406 (2007), the knowledge of such an artisan is part of the store of public knowledge that must be consulted when considering whether a claimed invention would have been obvious. *Randall Mfg. v. Rea*, 733 F.3d 1355, 1362-63 (Fed. Cir. 2013).

A. Multiple Sclerosis

Four types of MS are described in the medical literature: relapsing-remitting

("RR-MS"), secondary progressive ("SP-MS"), primary progressive ("PP-MS"), and progressive relapsing ("PR-MS"). EX1023 at 194-95; EX1002, ¶49. RR-MS is the most common form of the disease with approximately 85% of patients presenting with the RR-MS form at onset. EX1002, ¶49, discussing EX1005 at 161, 166, EX1023 at 201

Evidence gathered from the clinical evaluation of patients suggests that relapses are predominantly driven by inflammation, and disease progression is driven by neurodegeneration. EX1023 at 228-29, 564; *see also* Frohman, *et al.*, *Multiple Sclerosis – The Plaque and its Pathogenesis*, NEW ENGLAND JOURNAL OF MEDICINE, 354: 942-955 (2006) ("Frohman," EX1024) at 942; Kataoka, *et al.*, *FTY720, Sphingosine 1-Phosphate Receptor Modulator, Ameliorates Experimental Autoimmune Encephalomyelitis by Inhibition of T Cell Infiltration*, CELLULAR AND MOLECULAR IMMUNOLOGY, 2(6):439-448 (2005) ("Kataoka," EX1029) at 444-45; EX1002, ¶¶50, 53. Immunosuppressive therapies have been shown to be effective in treating RR-MS because such therapies reduce the inflammatory activity that leads to active lesions and relapses. EX1023 at 678; EX1002, ¶¶51-52. Purely progressive forms of the disease (SP-MS and PP-MS) are resistant to immunosuppressive therapies, consistent with progression being predominantly driven by neurodegeneration. EX1023 at 729-31; EX1024 at 942; *see also* "Clinical Pharmacology in the Critically Ill Child," in CRITICAL CARE PEDIATRICS,

Zimmerman and Gildea eds. (Saunders Company 1985) ("Critical Care," EX1021) at 954, 956; EX1002, ¶51.

B. Disease Modifying Therapies

Disease modifying therapies are given to patients for the purpose of reducing the frequency of relapses and delaying progression of a disease. EX1023 at 729-31; *see also* Inglese, *Multiple Sclerosis: New Insights and Trends*, AMERICAN JOURNAL OF NEURORADIOLOGY, 27: 954-957 (2006) ("Inglese," EX1025) at 956; EX1002, ¶53. Prior to 2006, little to no evidence suggested disease modifying therapies slowed MS disease progression directly. EX1023 at 732-33. However the art suggested that progression may be slowed indirectly by disease modifying therapies that reduce relapses and inflammatory disease activity. *Id.* Six FDA-approved disease modifying therapies for multiple sclerosis were available prior to the filing date of the '405 patent (beta-interferon-1a (Avonex®), beta-interferon-1a (Rebif®), beta-interferon-1b (Betaseron®), glatiramer acetate (Copaxone®), mitoxantrone (Novantrone®), and natalizumab (Tysabri®)) and were most effective in RR-MS patients. EX1023 at 758, 789-90; *see also* FDA approval letter for Tysabri®, ("Tysabri® Approval Letter," EX1036) at 1; EX1002, ¶¶53-54; EX1025 at 956.

C. Fingolimod

Fingolimod was derived from chemical modification of fungal metabolite ISP-1 in the mid-1990's. Adachi, *et al.*, *Design, Synthesis, and Structure-Activity Relationships of 2-Substituted-2-amino-1,3-propanediols: Discovery of a Novel Immunosuppressant, FTY720*, BIOORGANIC AND MEDICINAL CHEMISTRY LETTERS, 5(8):853-856 (1995) ("Adachi," EX1017) at 853; EX1002, ¶55. The hydrochloride salt of fingolimod, "FTY720 (2-amino-2-[2-(4-octylphenyl)ethyl]1,3-propanediol hydrochloride)" was taught by Adachi to have "displayed remarkable immunosuppressive activity both *in vitro* and *in vivo*." EX1017 at 853; EX1002, ¶¶55-56.

By the mid-1990's, those in the art reported that "FTY720 [] is expected [to be] a powerful candidate for safer immunosuppressant for organ transplantations and for the treatment of autoimmune diseases." EX1017 at 856; EX1002, ¶55; *see also* Chiba, *FTY720, a New Class of Immunomodulatory, Inhibits Lymphocyte Egress from Secondary Lymphoid Tissues and Thymus by Agonistic Activity at Sphingosine 1-Phosphate Receptors*, PHARMACOLOGY & THERAPEUTICS, 108:308-319 (2005) ("Chiba 2005," EX1022) at 309; Dumont, *Fingolimod Mitsubishi Pharma/Novartis*, IDRUGS, 8(3): 236-253 (2005) ("Dumont," EX1018).

Fingolimod hydrochloride was known as a potent agonist for sphingosine 1-phosphate (S1P) receptors. EX1018 at 236; EX1002, ¶55. S1P1 receptors,

expressed on lymphocytes and endothelial cells, were known to play a prominent role in lymphocyte trafficking and sequestration. *Id.* at 239. As an S1P agonist, FTY720 was known to cause sequestration of lymphocytes, decreasing the number of lymphocytes in the peripheral blood, and leading to lymphopenia. Yanagawa, *et al.*, *FTY720, a Novel Immunosuppressant, Induces Sequestration of Circulating Mature Lymphocytes by Acceleration of Lymphocyte Homing in Rats, III. Increase in Frequency of CD62L-Positive T Cells in Peyer's Patches by FTY720-Induced Lymphocyte Homing*, IMMUNOLOGY, 95: 591-594 (1998) ("Yanagawa," EX1020) at 591; EX1022 at 312; EX1002, ¶¶58-59, 63. Further, fingolimod was known to reduce infiltration of T cells, found at active disease sites in the brains of MS patients, into the central nervous system (CNS). Fujino, *et al.*, *Amelioration of Experimental Autoimmune Encephalomyelitis in Lewis Rats by FTY720 Treatment*, JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, 305(1):70-77 (2003) ("Fujino," EX1028) at 72-73; EX1002, ¶¶59, 64.

Prior to 2006, it was known that FTY720 was capable of inducing lymphopenia in oral doses as low as 0.125 mg per day. EX1002, ¶¶57, 65; Kahan, *et al.*, *Pharmacodynamics, Pharmacokinetics, and Safety of Multiple Doses of FTY720 in Stable Renal Transplant Patients: A Multicenter, Randomized, Placebo-Controlled, Phase I Study*, TRANSPLANTATION, 76(7):1079-1084 (2003) ("Kahan 2003," EX1031) at 1081.

Given its potent, yet reversible immunosuppressive properties, FTY720 was investigated as a treatment for a variety of immune-modulated diseases, including organ rejection and multiple sclerosis. EX1022 at 309; EX1002, ¶¶60-61, 63. Prior to the filing date of the '405 patent, much was known about the mechanism of action, pharmacokinetic/ pharmacodynamic properties, effective dosage amounts, dosage forms, and safety profile of fingolimod. *See*, generally, EX1018; EX1022. For instance, those in the art determined fingolimod hydrochloride's lymphopenia EC_{50} value (the dose which results in 50% of the maximum pharmacodynamic effect) was 0.5 mg/day. EX1019 at 691; EX1002, ¶62.

D. Loading Dose Regimens

Loading doses are sometimes used when a patient's condition requires immediate intervention and the drug used to treat the condition is slow to reach effective concentrations when administered at the maintenance dose level. EX1002, ¶¶68-69, citing "Introduction to Pharmacokinetics" in BIOPHARMACEUTICS AND CLINICAL PHARMACOKINETICS, Gibaldi (Lea & Febiger, 1991) ("Gibaldi," EX1034) at 12. Those in the art understood that the amount of a therapeutically effective maintenance dose is not dependent on employing a loading dose regimen. EX1002, ¶¶70-71, discussing EX1021 at 91, 94.

The art taught that when administering FTY720 to a patient undergoing an organ transplantation, "[t]he time needed to reach steady state is long, suggesting

the benefit of a loading dose." Kahan, B.D., *FTY720: A New Dimension in Transplantation*, TRANSPLANT. PROC., 33, 3081-3083 (2001) ("Kahan 2001," EX1027) at 3083; EX1002, ¶69. However, "[t]he use of a pharmacodynamic loading dose of FTY720" was indicated just for "certain situations where rapid attainment of decreased lymphocyte count is required (e.g. in the de novo transplant setting)." Dragun, D., *et al.*, *FTY720: Early Clinical Experience*, TRANSPLANT. PROC., 36 (Suppl 2S), 554S-548S (2004) ("Dragun," EX1026) at 546S; EX1002, ¶69.

Yet, the use of a loading dose regimen for FTY720 was known to be associated with adverse events. EX1002, ¶¶66, 72, citing EX1034 at 12; Kahan, B.D., *Sirolimus and FTY720: New Approaches to Transplant Immunosuppression*, TRANSPLANT. PROC., 34, 2520-2522 (2002) ("Kahan 2002," EX1030) at 2522. Those in the art taught that "[t]he primary side effect of FTY720 is bradycardia, which is at least partially dose-dependent, and is observed most commonly after administration of the loading dose" in transplant patients. EX1030 at 2522; EX1002, ¶¶66, 72. Additionally, no approved disease modifying therapy for MS employed a loading dose regimen before the effective filing date of the '405 patent. PHYSICIAN'S DESK REFERENCE, 59th Edition (Thomson PDR, January 1, 2005) ("PDR," EX1033) at 896, 954, 2625, 3120, 3224; EX1002, ¶¶67, 72.

VIII. DETAILED EXPLANATION OF GROUNDS FOR UNPATENTABILITY

A. [Ground 1] Claims 1-6 are Obvious under 35 U.S.C. § 103 over Kovarik and Thomson.

i. Claims 1, 3, and 5

Claim 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.

Claim 3:

> A method for treating Relapsing-Remitting multiple sclerosis in a subject in need thereof, . . . [same as body of claim 1].

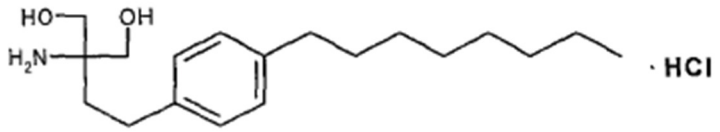
Claim 5:

> A method for slowing progression of Relapsing-Remitting multiple sclerosis in a subject in need thereof, . . . [same as body of claim 1].

Kovarik discloses sphingosine-1 phosphate ("S1P") receptor agonists that "elicit a lymphopenia resulting from a re-distribution, preferably reversible, of lymphocyte from circulation to secondary lymphatic tissue, without evoking a

generalized immunosuppression." EX1004 at 2. Given their ability to provoke a reversible lymphopenia, Kovarik teaches that the S1P receptor agonists can be used to treat transplant patients and "patients suffering from autoimmune diseases, e.g. multiple sclerosis[.]" *Id.* at 13-14; *see also* EX1002, ¶¶63-64, discussing EX1020 at 591 and EX1022 at 309; *id.* at ¶104. Kovarik teaches that the S1P receptor agonists are useful for the treatment of inflammatory and autoimmune diseases because of their "immune-modulating potency." EX1004 at 1.

Among these S1P agonist immunomodulators, Kovarik teaches a "particularly preferred S1P receptor agonist," "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, as shown:



." *Id.* at 13; EX1002, ¶104. As noted by Dr. Giesser, the compound shown above is referred to by those in the art as FTY720, or fingolimod hydrochloride, is the compound recited in claims 2, 4, and 6, and falls within the genus of compounds recited in claims 1, 3, and 5 of the '405 patent. EX1002, ¶104.

Kovarik specifically teaches that FTY720 may be administered orally (EX1004 at 18-19) and discloses daily dosages of FTY720 "for patients suffering from autoimmune diseases, e.g. multiple sclerosis[.]" *Id.* at 14-15; EX1002, ¶¶104, 106. Kovarik teaches a "maintenance therapy, e.g. a daily dosage of 0,5 mg," and describes a "method for treating an autoimmune disease in a subject in need thereof, comprising administering to the subject, after a loading regimen, a daily dosage of FTY720 of about 0.1 to 0.5 mg." EX1004 at 14, 17; *see also* EX1002, ¶105.

Kovarik describes a method whereby "a steady-state of the S1P receptor modulator or agonist blood levels is attained in less than a week." EX1004 at 15, ¶1.1; EX1002, ¶119. In contrast, the art taught that daily doses of FTY720 reach a steady-state concentration in about 4 weeks. EX1002, ¶57, citing EX1019 at 684. To achieve a more rapid attainment of a steady-state concentration of FTY720, Kovarik proposes to use a loading dose regimen. EX1004 at 1; *see also id.* at 15, ¶1.2 ("The use of a S1P receptor modulator or agonist, e.g. FTY720 . . . administered in such a way to a subject that a steady-state of the S1P receptor modulator or agonist blood levels is attained in less than a week."); *id.* at 16, ¶2 ("A method for inhibiting graft rejection or treating an autoimmune disease . . . comprising administering . . . FTY720, in such a pharmaceutically effective amount that a steady-state of the S1P receptor modulator or agonist blood levels is

attained in the subject in less than a week."); *id.* at 16, ¶2.1; *see also id.* at 20; EX1002, ¶¶119-20.

As noted by Dr. Giesser, however, data supporting any actual "benefit" of the loading dose regimen taught by Kovarik is conspicuously absent from the reference. EX1002, ¶¶79, 120, discussing EX1004, and the file history of its U.S. National Stage entry, U.S. Patent Application No. 11/720,205 ("the '205 Application," EX1014). Indeed, during prosecution, the examiner of the U.S. national stage entry of Kovarik wrote in a final office action:

> Applicant alleges that there is an unexpected advantage to having patients attain a steady state blood level earlier . . . However, a review of the specification, specifically, pages 18 and 19, recites procedures, e.g., loading regimen, but fails to provide data to support the allegation of unexpected results. Allegations without factual support are insufficient to support a finding of non-obviousness.

EX1014 at 0447; EX1002, ¶¶79, 123. The Applicants of the '205 application failed to respond or provide any further evidence of a "benefit" or unexpected results stemming from the adoption of a loading dose regimen, and the '205 application went abandoned. EX1014 at 0001; EX1002, ¶80. As noted by Dr. Giesser, she was unable to find any evidence published prior to the critical date suggesting that a loading dose regimen of

fingolimod hydrochloride resulted in any therapeutic benefit for multiple sclerosis patients. EX1002, ¶¶120-21.

Regardless of whether the loading dose regimen provides any unexpected benefit, it is clear that a loading dose regimen is not necessary for therapeutic efficacy in the treatment of MS with fingolimod or FTY720. EX1004 at 14; EX1002, ¶¶117-19, 121-22. Rather, Kovarik teaches that "the standard daily dosage (also called maintenance dose) refers to the dosage of an S1P receptor modulator or agonist necessary for a steady-state trough blood level of the medication or its active metabolite(s) providing effective treatment." EX1004 at 14, EX1002, ¶119. Thus, Kovarik discloses that the oral administration of a 0.5 mg daily dose of FTY720 provides effective treatment of multiple sclerosis regardless of whether a loading dose regimen is employed. EX1002, ¶119, discussing EX1004.

This conclusion is consistent with Applicants' own statements, which confirm that a maintenance dose is determined by the steady-state blood level required for efficacious treatment, and does not depend on a loading dose regimen for therapeutic efficacy. EX1010, the related '468 application file history, at 0109 (wherein Applicants assert the "standard daily dosage" is "the dosage necessary for a steady-state trough blood level of the drug providing effective treatment.").

As explained above (Section I.B.i), as well as by Dr. Giesser in her supporting declaration, loading dose regimens do not alter the equilibrium drug concentration associated with a daily dose. EX1002, ¶122; *see also* EX1034 at 12. To the contrary, the equilibrium drug concentration required for therapeutic efficacy is determined by the pharmacokinetic parameters of a drug having a particular potency, e.g., its absorption, distribution and elimination properties. EX1002, ¶¶28, 68, 122; EX1034 at 10; *see also* EX1021 at 93 ("[M]aintenance dose…is equal to the product of clearance…and [the] desired steady state plasma concentration.…"). Thus, the person of ordinary skill in the art would understand that the loading dose regimen taught by Kovarik is simply a method by which steady-state concentrations of FTY720 could be achieved in under a week, and not a prerequisite for therapeutic efficacy of the 0.5 mg FTY720 daily dose. EX1002, ¶¶119, 121-22, discussing EX1004.

That a loading dose regimen would not be a prerequisite for efficacy of an immunomodulatory agent such as fingolimod for the treatment of MS was confirmed by the indication of prior art DMTs for MS treatment without any immediately preceding loading dose regimen. EX1005 at 160; EX1002, ¶121, citing EX1033 at 896, 954, 2625, 3120, 3224 (listing the dosing regimens for Betaseron®, Avonex®, Rebif®, Novantrone®, and Copaxone®, which do not include loading dose regimens). As explained by Dr. Giesser, loading dose regimens were

not expected to be a prerequisite for effective immunomodulatory treatment of multiple sclerosis because immunomodulatory MS treatment was not typically indicated to resolve acute therapeutic urgency. EX1002, ¶119; EX1021 at 94. In contrast, those in the art recognized that loading doses were more likely to be appropriate in the context of organ transplantation. EX1002, ¶119, citing EX1027 at 3083, EX1026 at 546S ("The use of a pharmacodynamic loading dose of FTY720" was indicated for "certain situations where rapid attainment of decreased lymphocyte count is required (e.g. in the de novo transplant setting)." Because of the lack of similar therapeutic urgency for immunomodulatory treatment of RR-MS, no approved disease modifying therapy for RR-MS employed a loading dose regimen before the effective filing date of the '405 patent. EX1002, ¶¶119, 121; *see also* EX1033 at 896, 954, 2625, 3120, 3224 (listing the dosing regimens for Betaseron®, Avonex®, Rebif®, Novantrone®, and Copaxone®); EX1036 at 1; EX1025 at 956.

Indeed, the Applicants for the '405 patent noted during the prosecution of the related '468 application that treatment of MS does not require the same therapeutic urgency typical of organ transplant. *See* EX1010; EX1002, ¶¶21, 124. In responding to a non-final rejection, Applicants argued:

> When treating a transplant patient, it is important to deliver a very high dose very early in treatment to counter rejection of the transplanted tissue***, a consideration that does not apply to chronic***

> ***immune disorders such as multiple sclerosis,*** where the goal is to degrade the disease over the period of the patient's natural life.

EX1010 at 0110 (emphasis added).

Moreover, the background knowledge of one of skill in the art confirms that a single oral dose of 0.5 mg fingolimod is sufficient to significantly reduce peripheral blood lymphocyte counts within 6 hours of administration. EX1005 at 163. It also confirms that the nadir in lymphocyte counts (*i.e.*, full immunomodulatory impact) is reached after 4 days of treatment with fingolimod—long before steady-state levels are achieved. EX1002, ¶¶57, 60, citing EX1031 at 1084. Thus, the teachings of Kovarik and the background knowledge of a skilled artisan confirm that a loading dose regimen was not a prerequisite to therapeutic efficacy of an immunomodulatory treatment for MS, such as FTY720.

Because a loading dose regimen was not a prerequisite for therapeutic efficacy of fingolimod treatment of MS patients, it therefore would have been obvious to administer 0.5 mg FTY720 to an MS patient who is in need of immunomodulatory treatment absent an immediately preceding loading dose, even if another obvious choice would include employing a loading dose regimen.

In addition to having good reason to understand that a loading dose regimen was not required for therapeutic efficacy, however, the skilled artisan also would have had reason from the prior art to not use a loading

dose regimen when administering an immunomodulatory agent such as FTY720 for the treatment of MS. For example, loading dose regimens can be associated with significant adverse events because they include doses that are larger than maintenance doses. These increased risks must be balanced against any benefit attributable to decreasing the time to reaching therapeutic concentrations of the drug. EX1002, ¶125; EX1034 at 12 ("Loading of drugs may be hazardous, particularly for those drugs which distribute slowly or to which patients become accustomed only gradually. Caution should be applied at all times."). Indeed, adverse events associated with FY720 were known to be most often observed early in treatment and were associated with higher dosage levels. EX1002, ¶¶98, 125, discussing EX1030 at 2522. As noted by Dr. Giesser, those in the art taught that "[t]he primary side effect of FTY720 is bradycardia, which is at least partially dose-dependent, and is observed most commonly after administration of the loading dose" in transplant patients. EX1002, ¶¶98, 125, citing EX1030 at 2522.; *see also* EX1008 at 1075-76 (noting increased risk of bradycardia in human patients when FTY720 was administered at a daily dose greater than 0.5 mg). Thus, the risk of bradycardia at doses greater than 0.5 mg provided an additional reason to administer FTY720 for the treatment of MS absent an immediately preceding loading dose regimen.

Thus, the disclosures of Kovarik together with the background knowledge of the skilled artisan would have provided the artisan with a reasonable expectation of success in the treatment of multiple sclerosis with the daily oral administration of 0.5 mg of FTY720 without an immediately preceding loading dose regimen. EX1002, ¶125, discussing EX1004 at 15-16.

Moreover, Kovarik discloses at least one embodiment in which a 0.5 mg daily dose of fingolimod is administered absent an immediately preceding loading dose regimen. EX1004 at 15 (disclosing administration of 0.5 mg dose on the first day, increasing the daily dosage each day for the next three days, then returning to the 0.5 mg daily dose for maintenance therapy); EX1002, ¶126. Thus, day one of this treatment regimen taught by Kovarik is literally a 0.5 mg daily dose of fingolimod administered "absent an immediately preceding loading dose regimen" as recited by claims 1, 3, and 5 of the '405 patent. EX1002, ¶126.

A person of skill in that art would have read Kovarik's teachings as readily applicable to a patient with the RR-MS form of the disease because RR-MS is by far the most common form of the disease at onset and accounts for approximately 85% of cases. EX1005 at 161, 166; EX1002, ¶¶49, 107 discussing EX1023 at 201. Also, a skilled artisan would have known that inflammation is the driver of relapses in RR-MS (EX1002, ¶108; *id.* at ¶50, discussing EX1023 at 228-29) and that fingolimod hydrochloride was taught to treat MS by reducing inflammation

through the accelerated lymphocyte homing mechanism taught by Kovarik. EX1004, at 2; EX1002, ¶¶107-08; *see also* EX1018 at 236. Additionally, a skilled artisan would have appreciated that the purely progressive forms of MS, such as PP-MS and SP-MS, have been found refractory to treatment with immunomodulating agents. The artisan thus would have considered fingolimod as primarily applicable to the treatable (RR-MS) form of MS. EX1005 at 166; EX1002, ¶¶87, 107; *see also* EX1024 at 942; EX1029 at 444-45.

Thomson provides additional motivation to administer 0.5 mg FTY720 to a patient with RR-MS who is in need of treatment, of reducing, preventing, or alleviating relapses, and of slowing progression of RR-MS. Thomson presents an array of evidence supporting the efficacy of FTY720 in treating RR-MS by reducing relapse rates and slowing progression of RR-MS associated with inflammation. Based on the disclosures of Thomson, a person of ordinary skill would have had good reason to utilize the 0.5 mg daily dosage of FTY720 taught by Kovarik in the treatment of patients with RR-MS. EX1002, ¶109, discussing EX1005 at 158, 167.

Thomson teaches that FTY720 reduces inflammatory disease activity, which results in reduced relapse rates, increased time to first relapse, and increased intervals between relapses. EX1005 at 167; EX1002, ¶¶109-10. Thomson

concludes that "FTY720 has the potential to be an effective disease-modifying agent for the treatment of RRMS." *Id.*; EX1005 at 158.

Thomson also teaches that FTY720 reduces new and existing inflammatory lesions, which were utilized as markers for the manifestations of disease progression. EX1005 at 157-58; EX1002, ¶¶110-11. Thomson thereby teaches that there is a clinical benefit to treating RR-MS patients by administering FTY720, and that doing so reduces, prevents or alleviates the relapses and delays disease progression. EX1002, ¶¶87-88, 110-11; *see also* EX1018 at 238.

The skilled artisan would have had a reasonable expectation that the daily oral dose of 0.5 mg FTY720 taught by Kovarik would be therapeutically effective for patients suffering from RR-MS because Thomson describes clinical trials of FTY720 that tested doses in the range of 0.25 mg to 3.5 mg, in which it was found that "the actual degree of this property [lymphopenia] was similar across the range of doses used." EX1005 at 162-63; EX1002, ¶¶112-13.

While some clinical trials referenced by Thomson evaluated FTY720 in the context of organ transplantation, Thomson teaches their relevance to RR-MS treatment, noting that the "[p]harmacokinetic and pharmacodynamic outcomes . . . are not affected by disease status and may be extrapolated to include those patients with multiple sclerosis." EX1005 at 162; EX1002, ¶84. Thomson also notes that

"data derived from healthy subjects can be used to determine dosage guidelines for patients." EX1008 at 162; EX1002, ¶84.

Additionally, while some clinical trials discussed by Thomson used higher dosage amounts of FTY720, such as 1.25 mg and 5 mg, the skilled artisan would have recognized that lower doses, including 0.5 mg, produced similar immunomodulating effect as higher doses. EX1005 at 163 ("Although the higher doses of FTY720 produced a more rapid and sustained lymphocyte sequestration, the actual degree of this property was similar across the range of doses used in the study and no clear dose-response relationship was detected."); EX1002, ¶¶114-16. Indeed, it was known in the art that the 0.5 mg/day dose was the same as the EC_{50} value (the dose which results in 50% of the maximum pharmacodynamic effect). EX1002, ¶62, citing EX1019 at 691. Thus, the art taught no substantial immunomodulatory detriment to using lower doses, while teaching that lower doses decreased the risk of adverse effects such as bradycardia. EX1005 at 165; EX1002, ¶¶114-16; *see also* EX1030 at 2522. Thus, Thomson confirms that the 0.5 mg daily oral dose of FTY720 taught by Kovarik would be effective in the treatment (via relapse rate reduction and slowing the progression of RR-MS) of RR-MS. EX1002, ¶116.

Because both Kovarik and Thomson provide teachings regarding the therapeutic efficacy of FTY720 in the treatment of MS through its

immunomodulatory effect, and because of the reasonable expectation of therapeutic efficacy in RR-MS patients as discussed above, the skilled artisan would have been motivated to combine the teachings of Kovarik and Thomson. In so doing, the skilled artisan would arrive at the very same methods claimed in the '405 patent.

Thomson also provides additional reason to conclude that a person of ordinary skill in the art would have had good reason to administer FTY720 for the treatment of RR-MS without a preceding loading dose regimen. EX1002, ¶¶117-19, discussing EX1005. Thomson reports multiple clinical trials involving FTY720, and not even one of the trials describes administering a loading dose regimen of any kind. EX1005 at 163-65 & Tables 3-5; EX1002, ¶117.

In view of the discussion above, each of claims 1, 3, and 5 of the '405 patent is obvious under 35 U.S.C. § 103 in view of the teachings of Kovarik and Thomson. EX1002, ¶127. The claim chart below identifies exemplary places where the specific elements of claims 1, 3, and 5 are found in the references.

U.S Patent No. 9,187,405 Challenged Claims 1, 3, and 5	**Obvious over Kovarik (EX1004) and Thomson (EX1005)**
1. A method for reducing or preventing or alleviating relapses in Relapsing-Remitting multiple sclerosis in a subject in need thereof, 3. A method for treating	"Preferred medications [for] … patients suffering from autoimmune disease, e.g. multiple sclerosis …." EX1004 at 14; EX1002, ¶104. "A method for treating an autoimmune disease in a subject in need thereof, comprising administering…a daily dosage of FTY720 of

Relapsing-Remitting multiple sclerosis in a subject in need thereof, 5. A method for slowing progression of Relapsing-Remitting multiple sclerosis in a subject in need thereof,	about 0.1 to 0.5 mg." EX1004 at 17; EX1002, ¶106. "[W]hen compared with placebo treatment the annual relapse rate was significantly reduced … with FTY720…." EX1005 at 164-65; EX1002, ¶114. "Core emerging evidence summary for FTY720 in multiple sclerosis:… Reduction of new and existing inflammatory lesions responsible for subclinical disease progression." EX1005 at 157, Table 4; EX1002, ¶114.
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,	"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." EX1004 at 13; EX1002, ¶104. "[O]rally administered FTY720 achieved promising patient- and disease-oriented outcomes …." EX1005 at 164; EX1002, ¶¶109, 111.
at a daily dosage of 0.5 mg,	"Thereafter the treatment is continued with the maintenance therapy, e.g., a daily dosage of 0.5 mg." EX1004 at 15; EX1002, ¶105. "A method for treating an autoimmune disease in a subject in need thereof, comprising administering to the subject, after a loading regimen, a daily dosage of FTY720 of about 0.1 to 0.5 mg." EX1004 at 17; EX1002, ¶¶104-06; *see also* EX1004 at 15-16; EX1002, ¶¶105-06.
absent an immediately preceding loading dose regimen.	"[T]he standard daily dosage (also called maintenance dose) refers to the dosage of an S1P receptor modulator or agonist necessary for a steady-state trough blood level of the medication or its active metabolite(s) providing effective

	treatment." EX1004 at 14. None of the studies reported in Thomson report using a loading dose prior to administering FTY720 to treat MS or RR-MS. EX1005 at 164, 166-67, Table 3; EX1002, ¶117.

ii. Claims 2, 4, and 6

Dependent claims 2, 4, and 6 merely limit the administered form of fingolimod to fingolimod hydrochloride. The disclosures regarding fingolimod discussed above in Kovarik and Thomson were specifically for fingolimod hydrochloride. EX1004 at 13; EX1005 at 164; EX1002, ¶128.

In view of the discussion above, each of claims 2, 4, and 6 of the '405 patent is made obvious under 35 U.S.C. § 103 by the combined teachings of Kovarik and Thomson. EX1002, ¶¶128-29. The claim chart below identifies where the specific elements of claims 2, 4, and 6 are found in the references.

U.S Patent No. 9,187,405 Challenged Claims 2, 4, and 6	**Obvious over Kovarik (EX1004) and Thomson (EX1005)**
2. The method according to claim 1 wherein 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride is administered. 4. The method according to claim 3 wherein 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride is	"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, e.g., the hydrochloride." EX1004 at 13; EX1002, ¶128. "[O]rally administered FTY720 achieved promising patient- and disease-oriented outcomes …." EX1005 at 164; EX1002, ¶128.

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

B. [Ground 2] Claims 1-6 are Obvious under 35 U.S.C. § 103 over Chiba, Kappos 2005, and Budde.

As discussed in Ground 1, independent claims 1, 3, and 5 of the '405 patent recite a method comprising the oral administration of 0.5 mg fingolimod daily, absent an immediately preceding loading dose regimen, to a subject in need. Claim 1 recites a method for "reducing or preventing or alleviating relapses in Relapsing-Remitting multiple sclerosis," claim 3 recites the same steps for "treating Relapsing-Remitting multiple sclerosis," and claim 5 recites the same steps for "slowing progression of Relapsing-Remitting multiple sclerosis."

The Chiba patent discloses compounds that cause immunosuppression through accelerated lymphocyte homing, and a preferred immunomodulator in Chiba is fingolimod hydrochloride. EX1006 at 2:35-44; 4:63- 5:7; EX1002, ¶¶131-32. Chiba teaches that fingolimod hydrochloride has "superior immunosuppressive effects" and is useful "for the prevention or treatment of various indications such as immunosuppression in organ, cell or bone marrow transplantation, various autoimmune disease or various allergy diseases," including "multiple sclerosis." EX1006, 6:41-43; EX1002, ¶131.

In IPR2014-00784, one panel of the Board concluded that "Chiba itself suggested treating multiple sclerosis using a solid oral form of fingolimod." EX1032 at 10; EX1002, ¶132. Chiba teaches that S1P receptor agonists such as fingolimod hydrochloride may be administered "to an adult daily by 0.01 – 10 mg (potency) in a single dose." EX1006, 8:20-22; EX1002, ¶132. A skilled artisan would understand that the daily dosing regimen disclosed by Chiba does not employ an immediately preceding loading dose regimen as none is indicated. EX1006, col. 8, ll. 29-34; EX1002, ¶132. Further, as noted by Dr. Giesser, she was unable to find any evidence published prior to the critical date suggesting that a loading dose regimen of fingolimod hydrochloride resulted in any therapeutic benefit for multiple sclerosis patients. EX1002, ¶¶120-21.

A person of skill in the art would have read Chiba's teachings regarding the use of fingolimod hydrochloride for the treatment of MS as readily applicable to a patient with the RR-MS form of the disease. EX1002, ¶133, discussing EX1006. RR-MS is by far the most common form of the disease at onset and accounts for approximately 85% of cases. EX1002, ¶¶49, 136, discussing EX1023 at 201. Also, a skilled artisan would have known that inflammation is the driver of relapses in RR-MS (EX1002, ¶136, discussing EX1023 at 228-29), and fingolimod hydrochloride was taught to reduce inflammation through the accelerated

lymphocyte homing mechanism taught by Chiba. EX1006 at 2:59-3:6; *id.* at 4:64-67; EX1002, ¶136. Finally, a skilled artisan would have known that the purely progressive forms of MS, such as PP-MS and SP-MS, had been found refractory to treatment with immunomodulating agents and would have considered fingolimod as primarily applicable to the treatable (RR-MS) form of MS. EX1002, ¶¶51, 133; *see also* EX1018 at 236; EX1024 at 942. The skilled artisan thus would have been motivated to consider literature reporting clinical efficacy of FTY720 among RR-MS patients, such as that reported in Kappos 2005.

Kappos 2005 discloses the results of a Phase II randomized, double-blind, placebo-controlled study sponsored by Novartis AG. EX1007 at 41, abstract O141. At the two doses tested (1.25 mg and 5.0 mg), Kappos 2005 teaches that fingolimod hydrochloride is efficacious for treatment of relapsing MS, as measured by inflammation (MRI) and relapse-related endpoints. EX1007 at 41, abstract O141; EX1002, ¶134. Kappos 2005 teaches that fingolimod hydrochloride was well-tolerated and that "[t]here was no compelling dose-related difference in efficacy on MRI or clinical endpoints." EX1007 at 41, abstract O141; EX1002, ¶¶134-35. Kappos 2005 teaches that the results of the trial "strongly suggest that FTY720 has the potential to be an efficacious disease modifying treatment for relapsing forms of MS with the additional benefit of once daily administration. EX1007 at 41, abstract O141; EX1002, ¶¶134-36.

Based on Kappos 2005's results from using FTY720 for the treatment of the relapsing form of multiple sclerosis, a person of ordinary skill in the art would have had a reasonable expectation of success in applying Chiba's teaching to treat MS with a daily dose of 0.01-10 mg fingolimod hydrochloride to treating RR-MS patients. EX1002, ¶136, discussing EX1006, EX1007, EX1023 at 201. Fingolimod was known to be a potent immunosuppressant (EX1006, 6: 26-31) and RR-MS was known to respond to treatment with immunosuppressants. EX1002, ¶¶54 (noting that "[a]ll disease modifying therapies approved as of June 27, 2006 are immune modulators or immunosuppressants and all are most effective in RR-MS patients"), 55; *see also* EX1023 at 758, 789-790, 793; EX1017 at 856; EX1033 at 896, 954, 2625, 3120, 3224; EX1036 at 1; EX1025 at 956. Further, T cells were known to be present at active disease sites in the brains of MS patients, and fingolimod was known to reduce infiltration of T cells into the CNS. EX1002, ¶63, discussing EX1028 at 72-73; *see also* EX1002, ¶¶58, 60-61, 64, 84, citing EX1022 at 309, EX1018 at 237-39, EX1019 at 684, EX1031 at 1081, EX1028 at 440, and identifying lymphopenia as "relevant for relating dosage to lymphopenia for MS." Thus, a skilled artisan would have reasonably applied the teachings of Chiba to treat MS using FTY720 to the teachings of Kappos 2005 to treat RR-MS using FTY720. EX1002, ¶136.

As discussed more fully below, it was known in the prior art to treat RR-MS with fingolimod because fingolimod was known to reduce, prevent, or alleviate relapses in RR-MS patients and because relapses were known to contribute to disease progression. EX1002, ¶¶137-38. Kappos 2005 explicitly teaches that fingolimod hydrochloride reduces and prevents relapses and that it is an "efficacious disease modifying treatment for relapsing forms of MS." *Id.*; EX1007 at 41, abstract O141. Kappos 2005 teaches that fingolimod hydrochloride reduced the relapse rate and also decreased the number and volume of inflammatory lesions in the brain (the sites of demyelination). *Id.*; EX1002, ¶138, also citing EX1023 at 193, and explaining "RR-MS increases in lesion volume or number contribute to patient disability over time . . . Therefore a person of ordinary skill in the art would have appreciated that FTY720 was useful for administration to RR-MS patients who had a need for 'slowing the progression' of RR-MS."

Kappos 2005 discloses daily doses of 1.25 mg and 5.0 mg but teaches that there are no significant differences in clinical or disease-related endpoints between the two doses. EX1007 at 41, abstract O141; EX1002, ¶¶134-35. Moreover, Budde describes a dose ranging trial (0.25 mg to 3.5 mg) in which it was found that the degree of lymphopenia was similar across the range of doses tested. EX1008 at 1079. As stated by a panel of the Board reviewing Budde's teachings in a separate IPR proceeding, "Budde describes a clinical effect of a low dose of

fingolimod." EX1032 at 52. Indeed, Budde reports that a 0.5 mg dose of FTY720 was efficacious in producing a reversible lymphopenia, yet was associated with fewer adverse events than higher doses. EX1008 at 1083 (stating that "[s]ingle oral doses of FTY[720] in doses ranging from 0.5 mg to 3.5 mg caused a dose-dependent, reversible lymphopenia," and "higher doses caused a more rapid and more sustained lymphopenia, however the degree of lymphopenia showed only minor differences."); *id.* at 1075 (noting that "[h]igher doses of FTY[720] were more frequently associated with bradycardia: 9 out of 12 subjects randomized to ≥0.75 mg of FTY[720] developed bradycardia; however, only 1 of 12 subjects receiving 0.25 to 0.5 mg of FTY[720 developed bradycardia]."); EX1002, ¶¶139-40.

In view of Kappos 2005 and Budde, the skilled artisan would have a reasonable expectation that the 0.5 mg daily dose, a dose within the range taught by Chiba and specifically used by Budde, would induce the desired pharmacological effect (lymphopenia) in RR-MS patients. EX1002, ¶¶58, 60-61, 64, 84, 139, citing EX1022 at 309, EX1018 at 237-39, EX1019 at 684, EX1031 at 1081, EX1028 at 440, and identifying lymphopenia as being "often used as a clinical end-point in dose response studies" and "relevant for relating dosage to lymphopenia for MS." Thus, a skilled artisan would have had reason to use the 0.5 mg dose identified in these clinical trials because there was no substantial

pharmacological detriment to using the lower 0.5 mg dose and because Budde teaches that the 0.5 mg dose was associated with a decreased risk of adverse effects such as bradycardia when compared to higher doses. EX1008 at 1075-76; EX1002, ¶139.

Because Chiba teaches oral administration of fingolimod hydrochloride for the treatment of multiple sclerosis, with Kappos 2005 confirming its utility in RR-MS patients and Budde confirming the efficacy of a 0.5 mg daily dose of FTY720, each of claims 1, 3, and 5 of the '405 patent is made obvious under 35 U.S.C. §103 by the combined teachings of Chiba, Kappos 2005, and Budde. EX1002, ¶141.

The claim chart below identifies where the specific elements of claims 1, 3, and 5 are found in Chiba, Kappos 2005, and Budde.

U.S Patent No. 9,187,405 Challenged Claims 1, 3, and 5	**Obvious over Chiba (EX1006), Kappos 2005 (EX1007) and Budde (EX1008)**
1. A method for reducing or preventing or alleviating relapses in Relapsing-Remitting multiple sclerosis in a subject in need thereof, 3. A method for treating Relapsing-Remitting multiple sclerosis in a subject in need thereof, 5. A method for slowing progression of Relapsing-Remitting multiple sclerosis in a subject in need thereof,	"Namely, the compositions of the present invention have pharmacological activities such as immunosuppressive activity … and therefore are useful for the prevention or treatment of … autoimmune diseases such as … multiple sclerosis[.]" EX1006, 6:31-43; EX1002, ¶131. "[C]learly significant effects favoring both FTY720 groups vs. PL were found for Gd-enhancing lesion volume, new T2 lesions and change in T2 lesion volume[.]" EX1007 at 41, abstract O141; EX1002, ¶135. "The proportion of relapse-free patients …, annualized relapse rate … and time to first

	relapse were significantly better in both FTY720 groups vs. [placebo].” EX1007 at 41, abstract O141; EX1002, ¶135.
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,	“The examples below detail the use of FTY720 by oral administration.” EX1006, 11:20-22; EX1002, ¶132. “FTY720 is an oral immunomodulator ….” EX1007 at 41, abstract O141; EX1002, ¶134. “This study used a randomized, double-blind, placebo-controlled design that explored single oral doses of FTY720[.]” EX1008 at 1073; EX1002, ¶139.
at a daily dosage of 0.5 mg,	“[T]he 2-aminopropane-1,3-diol compound [*e.g.*, FTY720] . . . may be administered for example, to an adult daily by 0.01-10 mg (potency) in a single dose[.]”EX1006, 8:19-34; EX1002, ¶¶90-92, 132. “The doses selected for the study were 0.25, 0.5, 0.75, 1.0, 2.0, and 3.5 mg.” EX1008 at 1074; EX1002, ¶139. “All treated groups, 0.25 to 3.5 mg of FTY720, consistently manifested a more pronounced decrease in lymphocyte counts compared with the placebo group.” EX1008 at 1078; EX1002, ¶139. “At FTY doses ranging from 0.5 mg to 3.5 mg, no clear dose response relationship was detected, but the two highest dose groups exhibited a more pronounced decline in lymphocyte numbers.” EX1008 at 1079; EX1002, ¶139. “281 patients with active relapsing MS were randomized to receive PL [(placebo)] (n=93), 1.25 mg (n=94) or 5.0 mg FTY720 (n=94) . . .

	There was no compelling dose-related difference in efficacy on MRI or clinical endpoints." EX1007 at 41, abstract O141; EX1002, ¶135. "Higher doses of FTY were more frequently associated with bradycardia: 9 out of 12 subjects randomized to ≥0.75 mg of FTY developed bradycardia." EX1008 at 1075; EX1002, ¶139. "Patients treated with ≥0.75 mg of FTY had a more pronounced decline in heart rate." EX1008 at 1076; EX1002, ¶139.
absent an immediately preceding loading dose regimen.	None of Chiba, Kappos 2005, or Budde described or suggest using a loading dose prior to administering FTY720 to treat MS or RR-MS.

i. Claims 2, 4, and 6

Claims 2, 4, and 6 merely limit the administered form of fingolimod to fingolimod hydrochloride. As discussed above, Chiba, Kappos 2005, and Budde explicitly disclose administration of fingolimod hydrochloride. EX1006, 11:28-31; EX1007 at 41, abstract O141; EX1008 at 1073; EX1002, ¶¶142-43. Thus, in view of the discussion above regarding claims 1, 3, and 5, each of claims 2, 4, and 6 of the '405 patent is also made obvious under 35 U.S.C. § 103 by the combined teachings of Chiba, Kappos 2005, and Budde. EX1002, ¶143. The claim chart below identifies where the specific elements of claims 2, 4, and 6 are found in the references.

U.S Patent No. 9,187,405 Challenged Claims 2, 4, and 6	Obvious over Chiba (EX1006), Kappos 2005 (EX1007) and Budde (EX1008)
2. The method according to claim 1 wherein 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride is administered. 4. The method according to claim 3 wherein 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride is administered. 6. The method according to claim 5 wherein 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride is administered.	"… introducing an effective amount of an accelerated lymphocyte homing composition comprising 2-amino-2[2-(4-octylphenyl)ethyl]propane-1,2-diol hydrochloride[.]" EX1006, 24:65-67; EX1002, ¶¶142-43. "… FTY720 has the potential to be an efficacious disease modifying treatment for relapsing forms of MS with the additional benefit of once daily oral administration." EX1007 at 41, abstract O141. "This study used a randomized, double-blind, placebo-controlled design that explored single oral doses of FTY720[.]" EX1008 at 1073; EX1002, ¶¶142-43.

C. [Ground 3] Claims 1-6 are Anticipated under 35 U.S.C. § 102 by Kappos 2010 (EX1038)

As noted above in Section I.D.vi, claims 1-6 are not entitled to a filing date earlier than the April 21, 2014 filing date of the '342 application because the claim limitation that fingolimod is administered "absent an immediately preceding loading dose regimen" first appeared in the '342 application in a preliminary amendment. EX1011 at 0079-81. The originally filed '342 application is silent on whether or not to use a loading dose regimen. EX1002, ¶¶15, 144; EX1011 at 0111-27. The applications to which the '342 claim priority, *i.e.*, U.S. Patent Application Nos. 13/149,468, filed on May 31, 2011, and 12/303,765, filed on June

25, 2007, and Great Britain Application No. 0612721.1 filed on June 27, 2006, are also silent regarding loading dose regimens. EX1002, ¶144; EX1012 (GB 0612721.1); EX1009 (File History U.S. Pat. Appl. No. 12/303,765); EX1010 (File History U.S. Pat. Appl. No. 13/149,468).

In the ’405 patent, each of independent claims 1, 3 and 5 contain the negative limitation of “absent an immediately preceding loading dose regimen limitation.” EX1001, 12:49-13:9. Because these claims of the ’405 patent are entitled to a priority date no earlier than the April 21, 2014 filing date of the ’342 application, documents published before April 21, 2013, are prior art to and may be applied against the claims of the ’405 patent under 35 U.S.C. § 102(b) in this Ground 3.

As shown below, each and every element recited in claims 1-6 of the ’405 patent is disclosed by Kappos 2010 (EX1038). Thus, claims 1-6 are anticipated under 35 U.S.C. § 102(b). As discussed in Ground 1, independent claims 1, 3, and 5 of the ’405 patent recite a method comprising the oral administration of 0.5 mg fingolimod daily, absent an immediately preceding loading dose regimen, to a subject in need. Claim 1 recites that the method is for “reducing or preventing or alleviating relapses in Relapsing-Remitting multiple sclerosis,” claim 3 recites the same method for “treating Relapsing-Remitting multiple sclerosis,” and claim 5

recites the same method for "slowing progression of Relapsing-Remitting multiple sclerosis."

Kappos 2010 discloses the results of a "phase 3, double-blind, placebo-controlled study, called FREEDOMS (FTY720 Research Evaluating Effects of Daily Oral therapy in Multiple Sclerosis)." EX1038 at 388; EX1002, ¶145. In this study, RR-MS patients were assigned randomly to "receive oral fingolimod capsules in a dose of 0.5 mg or 1.25 mg or matching placebo, once daily for 24 months." EX1038 at 388; EX1002, ¶145. Kappos 2010 does not recite a loading dose regimen. EX1038 at 388; EX1002, ¶145. Kappos 2010 concludes that fingolimod was effective in reducing relapses in RRMS patients (as recited in claim 1), as follows:

> [O]ral fingolimod as compared with placebo had superior efficacy in this 24-month study involving patients with relapsing–remitting multiple sclerosis. Rates of relapse, progression of clinical disability, and MRI evidence of inflammatory lesion activity and tissue destruction were all significantly reduced with the use of fingolimod. The two doses of fingolimod had similar efficacy, and adverse events may be less frequent with the 0.5-mg dose than with the 1.25-mg dose. Thorough observation and long-term follow-up are necessary for a more informed assessment of the benefits and risks of this new treatment option for relapsing multiple sclerosis.

EX1038 at 400; EX1002, ¶145. Kappos 2010 also discloses that daily oral administration of 0.5 mg fingolimod is a treatment for RR-MS, and thus anticipates claim 3. Kappos 2010 further states that fingolimod "significantly reduced" "progression of clinical disability," thus anticipating claim 5. *Id*. at 390, 400.

U.S Patent No. 9,187,405 Challenged Claims 1, 3, and 5	**Anticipated by Kappos 2010 (EX1038)**
1. A method for reducing or preventing or alleviating relapses in Relapsing-Remitting multiple sclerosis in a subject in need thereof, 3. A method for treating Relapsing-Remitting multiple sclerosis in a subject in need thereof, 5. A method for slowing progression of Relapsing-Remitting multiple sclerosis in a subject in need thereof,	"The aggregate annualized relapse rate was lower with fingolimod at a dose of 0.5 mg … that with placebo …." EX1038 at 390 (parentheticals omitted). "In the fingolimod groups as compared with the placebo group, the time to a first relapse was longer, the risk of relapse was reduced, and proportionately more patients remained free of relapse during the 24-month period. *Id*. (parentheticals omitted); EX1002, ¶145. "The time to disability progression … was longer with both fingolimod doses than with placebo…." EX1038 at 390; EX1002, ¶145.
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,	"Patients received oral fingolimod at a dose of 0.5 mg …" *Id*. at 387; EX1002, ¶145.
at a daily dosage of 0.5 mg,	"Patients received oral fingolimod at a dose of 0.5 mg …" *Id*. at 387; EX1002, ¶145.
absent an immediately preceding loading dose regimen.	Kappos 2010 does not report using a loading dose prior to administering FTY720 to treat RR-MS:

	"Patients were randomly assigned … to receive oral fingolimod capsules in a dose of 0.5 mg or 1.25 mg or matching placebo, once daily for 24 months." EX1038 at 388; EX1002, ¶145.

i. Claims 2, 4, and 6

Dependent claims 2, 4, and 6 limit the administered form of fingolimod to fingolimod hydrochloride. The clinical trial disclosed in Kappos 2010 was named FREEDOMS, an acronym for FTY720 Research Evaluating Effects of Daily Oral therapy in Multiple Sclerosis, and FTY720 is referred to throughout Kappos 2010. EX1038 at 387-88; EX1002, ¶146. Thus the form of fingolimod administered to the RR-MS patients in the clinical trial, FTY720, was the hydrochloride salt. EX1002, ¶146, *see also* EX1017 at 853. As such, each of claims 2, 4, and 6 of the '405 patent is anticipated under 35 U.S.C. § 102(b).

IX. NO EVIDENCE OF UNEXPECTED RESULTS OR SECONDARY CONSIDERATIONS ARE ATTRIBUTABLE TO NOVEL ASPECTS OF THE CLAIMS

A *prima facie* case of obviousness may in some instances be rebutted by such "secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc." *Graham v. John Deere Co. of Kansas City*, 383 US 1, 17-18 (1966). These factors are relevant to a determination of obviousness to the extent that they can be linked to novel and claimed features. *See*, *e.g.*, *Tokai Corp. v. Easton Enterprises, Inc.*, 632 F. 3d 1358, 1369 (Fed. Cir. 2011) ("If commercial success is due to an element in the prior art, no nexus exists."); *Richdel, Inc. v.*

Sunspool Corp., 714 F.2d 1573, 1580 (Fed. Cir.1983) (Claims were obvious because patent owner "failed to show that such commercial success … was due to anything disclosed in the patent in suit which was not readily available in the prior art.").

No evidence relating to the claimed dosage regimen, much less a comparison with prior art dosage regimens, was presented in the specification of the '405 patent, in its priority documents, or during prosecution. EX1002, ¶¶147, 149, discussing EX1012; EX1009; EX1010; EX1011. As a result, there is no known evidence to support a claim of unexpected results. *Id.*

In another IPR proceeding not involving the '405 patent or the present Petitioners, a panel of the Board considered secondary indicia evidence related to Gilenya®, the only fingolimod product approved by the FDA for the treatment of multiple sclerosis. *See* EX1035 (Orange Book entry for Fingolimod); EX1002, ¶148. In IPR2014-00784, the Board concluded that Patent Owner's purported evidence of secondary indicia could not be attributed to anything other than the prior art solid oral dosage form of fingolimod used for the treatment of MS, as disclosed in Chiba (EX1006). EX1032 (Final Written Decision, Paper 112) at 21-30; EX1002, ¶¶149-50. The same conclusion holds here: Any need for an oral dosage form for treating MS was satisfied by the disclosures of each of Chiba, Budde, Kappos 2005, Kovarik, and Thomson. *Id.* Likewise, any industry praise

for Gilenya® is also attributable to the prior art disclosure of using solid oral dosage form of fingolimod for the treatment of RR-MS. *Id.* at ¶¶148-50.

In sum, while the patent owner may point to Gilenya® as the commercial embodiment of the claims, there is no secondary indicia evidence that may be attributed to the dosing regimen claimed in the ’405 patent separately from the prior art disclosures of using FTY720 to treat RR-MS. *Id.*

X. CONCLUSION

For the reasons set forth above, claims 1-6 of the ’405 patent are unpatentable. Petitioners therefore request that an *inter partes* review of these claims be instituted.

Respectfully submitted,

Dated: February 3, 2017

/ Steven W. Parmelee /
Steven W. Parmelee, Lead Counsel
Reg. No. 31,990

XI. CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. §42.24(d), the undersigned certifies that this Petition complies with the type-volume limitation of 37 C.F.R. §42.24(a). The word count application of the word processing program used to prepare this Petition indicates that the Petition contains 13,584 words, excluding the parts of the brief exempted by 37 C.F.R. §42.24(a).

Respectfully submitted,

Dated: February 3, 2017

/ Steven W. Parmelee /
Steven W. Parmelee, Lead Counsel
Reg. No. 31,990

XII. PAYMENT OF FEES UNDER 37 C.F.R. §§ 42.15(A) AND 42.103

The required fees are submitted herewith. If any additional fees are due at any time during this proceeding, the Office is authorized to charge such fees to Deposit Account No. 23-2415.

XIII. APPENDIX – LIST OF EXHIBITS

Exhibit No.	Description
1001	U.S. Patent No. 9,187,405, "S1P Receptor Modulators for Treating Relapsing-Remitting Multiple Sclerosis" (filed April 21, 2014) (issued November 17, 2015)
1002	Declaration of Dr. Barbara S. Giesser
1003	*Curriculum Vitae* of Dr. Barbara S. Giesser
1004	John Kovarik and Silke Appel-Dingemanse: International Publication No. WO 2006/058316 (published June 1, 2006)
1005	Thomson, *FTY720 in Multiple Sclerosis: The Emerging Evidence of its Therapeutic Value*, CORE EVIDENCE, 1(3):157-167 (2006)
1006	U. S. Patent No. 6,004,565 (Chiba) "Compositions and Methods of Using Compositions with Accelerated Lymphocyte Homing Immunosuppressive Properties" (filed September 23, 1997) (issued December 21, 1999)
1007	Kappos, L., *et al.*, *FTY720 in Relapsing MS: Results of a Double-Blind Placebo-Controlled Trial with a Novel Oral Immunomodulator*, JOURNAL OF NEUROLOGY 252(Suppl 2):11/41, Abstract O141 (2005)
1008	Budde, *et al.*, *First Human Trial of FTY720, a Novel Immunomodulatory, in Stable Renal Transplant Patients*, JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY, 13:1073-1083 (2002)
1009	File History U.S. Patent Application No. 12/303,765
1010	File History U.S. Patent Application No. 13/149,468
1011	File History U.S. Patent Application No. 14/257,342
1012	GB 0612721.1
1013	U.S. Pat. No. 8,741,963 "S1P Receptor Modulators for Treating Multiple Sclerosis" (filed May 31, 2011) (issued June 3, 2014)

1014	File History of U.S. Patent Application No. 11/720,205
1015	Provisional Patent Application No. 60/631,483 (filed November 29, 2004)
1016	Virley, *Developing Therapeutics for the Treatment of Multiple Sclerosis*, NEURORX, 2:638-649 (2005)
1017	Adachi, *et al.*, *Design, Synthesis, and Structure-Activity Relationships of 2-Substituted-2-amino-1,3-propanediols: Discovery of a Novel Immunosuppressant, FTY720*, BIOORGANIC AND MEDICINAL CHEMISTRY LETTERS, 5(8):853-856 (1995)
1018	Dumont, *Fingolimod Mitsubishi Pharma/Novartis*, IDRUGS, 8(3):236-253 (2005)
1019	Park, *et al.*, *Pharmacokinetic/Pharmacodynamic Relationships of FTY720 in Kidney Transplant Patients*, BRAZILIAN JOURNAL OF MEDICAL AND BIOLOGICAL RESEARCH, 38: 683-694 (2005)
1020	Yanagawa, *et al.*, *FTY720, a Novel Immunosuppressant, Induces Sequestration of Circulating Mature Lymphocytes by Acceleration of Lymphocyte Homing in Rats, III. Increase in Frequency of CD62L-Positive T Cells in Peyer's Patches by FTY720-Induced Lymphocyte Homing*, IMMUNOLOGY, 95: 591-594 (1998)
1021	"Clinical Pharmacology in the Critically Ill Child," in CRITICAL CARE PEDIATRICS, Zimmerman and Gildea eds. (Saunders Company 1985)
1022	Chiba, *FTY720, a New Class of Immunomodulatory, Inhibits Lymphocyte Egress from Secondary Lymphoid Tissues and Thymus by Agonistic Activity at Sphingosine 1-Phosphate Receptors*, PHARMACOLOGY & THERAPEUTICS, 108:308-319 (2005)
1023	MCALPINE'S MULTIPLE SCLEROSIS, 4th Edition, Compston, ed (Elsevier, Inc., December 2005)
1024	Frohman, *et al.*, *Multiple Sclerosis – The Plaque and its Pathogenesis*, NEW ENGLAND JOURNAL OF MEDICINE, 354: 942-955 (2006)

1025	Inglese, *Multiple Sclerosis: New Insights and Trends*, AMERICAN JOURNAL OF NEURORADIOLOGY, 27: 954-957 (2006)
1026	Dragun, D., *et al.*, *FTY720: Early Clinical Experience*, TRANSPLANT. PROC., 36 (Suppl 2S), 554S-548S (2004)
1027	Kahan, B.D., *FTY720: A New Dimension in Transplantation*, TRANSPLANT. PROC., 33, 3081-3083 (2001)
1028	Fujino, *et al.*, *Amelioration of Experimental Autoimmune Encephalomyelitis in Lewis Rats by FTY720 Treatment*, JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, 305(1):70-77 (2003)
1029	Kataoka, *et al.*, *FTY720, Sphingosine 1-Phosphate Receptor Modulator, Ameliorates Experimental Autoimmune Encephalomyelitis by Inhibition of T Cell Infiltration*, CELLULAR AND MOLECULAR IMMUNOLOGY, 2(6):439-448 (2005)
1030	Kahan, B.D., *Sirolimus and FTY720: New Approaches to Transplant Immunosuppression*, TRANSPLANT. PROC., 34, 2520-2522 (2002)
1031	Kahan, *et al.*, *Pharmacodynamics, Pharmacokinetics, and Safety of Multiple Doses of FTY720 in Stable Renal Transplant Patients: A Multicenter, Randomized, Placebo-Controlled, Phase I Study*, TRANSPLANTATION, 76(7): 1079-1084 (2003)
1032	Final Written Decision, Paper 112, IPR2014-00784
1033	PHYSICIAN'S DESK REFERENCE, 59th Edition (Thomson PDR, January 1, 2005)
1034	"Introduction to Pharmacokinetics" in BIOPHARMACEUTICS AND CLINICAL PHARMACOKINETICS, Gibaldi (Lea & Febiger, 1991)
1035	Orange Book entry for Fingolimod (http://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=001&Appl_No=022527&Appl_type=N) (last accessed February 2, 2017)

1036	FDA approval letter for Tysabri, obtained from the Food and Drug Administration website http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=125104 (last accessed January 30, 2017)
1037	U. S. Pat. No. 8,324,283 (Oomura) *Solid Pharmaceutical Compositions Comprising a SIP Receptor Agonist and a Sugar Alcohol* (filed August 11, 2008) (issued December 4, 2012)
1038	Kappos, L., *et al.*, *A Placebo-Controlled Trial of Oral Fingolimod in Relapsing Multiple Sclerosis*, NEW ENGLAND JOURNAL OF MEDICINE, 362(5):387-401 (2010)
1039	LaMontagne, *et al.*, "Antagonism of Sphingosine-1-Phosphate Receptors by FTY720 Inhibits Angiogenesis," *Cancer Res.*, 66:221-231 (Jan. 2006)
1040	Thomson, *FTY720 in Multiple Sclerosis: The Emerging Evidence of its Therapeutic Value*, CORE EVIDENCE, 1(3):157-167 (2006)

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), this is to certify that I caused to be served a true and correct copy of the foregoing Petition for *inter partes* review of U.S. Patent No. 9,187,405 (and accompanying Exhibits 1001-1040) by overnight courier (Federal Express), on this 3rd day of February, 2017, on the Patent Owner at the correspondence address of the Patent Owner as follows:

Novartis Pharmaceutical Corporation
Intellectual Property Department
One Health Plaza 433/2
East Hanover, NJ 07936-1080

Respectfully submitted,

Dated: February 3, 2017

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