IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF	Art Unit: 1629
Hiestand, Peter C. et al.	Examiner: Weddington, Kevin E
APPLICATION NO: 14/257342	Conf. No.: 7853
FILED: April 21, 2014	
FOR: S1P Receptor Modulators for Treating Multiple Sclerosis	

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

AMENDMENT

Sir:

This Reply is submitted in response to the Office Action mailed April 6, 2015. Reconsideration and withdrawal of the present rejections are respectfully requested.

A courtesy copy of the Claims begins on page 2 of this paper.

Remarks/Arguments begin on page 3 of this paper.

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

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

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

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

4. (previously presented) The method according to claim 3 wherein ~~the S1P receptor modulator is~~ 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride is administered.

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

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

Remarks/Arguments

Reconsideration of the above application is respectfully requested.

Claims 1-6 are pending in this application.

In the Office Action, claims 1-6 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Virley, D.J., Journal of the American Society for NeuroTherapeutics ("Virley"), in view of Kovarik *et al.*, WO06/058316 ("Kovarik"), both of record. The Examiner stated that Virley teaches 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol (FTY720) as an agent for the treatment of Relapsing-Remitting multiple sclerosis ("RRMS"). The Examiner acknowledges that Virley does not teach the claimed daily dose of 0.5 mg, and relies on Kovarik to cure this deficiency of Virley. More specifically, the Examiner contends that Kovarik teaches the claimed daily dosage of about 0.5 mg, at p. 17, line 16. For the following reasons, Applicants traverse this rejection, as applied to all pending claims, as amended, and respectfully request that it be withdrawn.

The pending claims (or the claims from which they depend) specify that the stated daily dosage of 0.5 mg cannot immediately follow a loading dose regimen. Kovarik does not teach or suggest ***any*** daily does of FTY720 that does not immediately follow a loading dose regimen and, indeed, relies upon the disclosed loading does regimen to determine the daily dose that follows it.

More specifically, Kovarik's mention of a dosage of 0.5 mg is limited to the context of a dosage that follows, immediately, the loading dose regimen described therein. Indeed, the very passage cited by the Examiner. P. 17, line 16, specifies that a daily dosage of 0.1 to 0.5 mg ***follows a loading regimen***. The Kovarik loading dose regimen involves raising stepwise the daily dosage of the S1P receptor or agonist over 3 to 6 days up to 3- to 21-fold the standard daily dosage for the purpose of attaining steady state blood levels of the drug in less than a week. This loading dosage allows patients to continue, immediately following such regimen, with a daily dosage that is the same or lower than the standard daily dosage. Kovarik indicates that when the dosage administered after the initial period is lower than the standard daily dosage, it can be from 1/50 to ½ the standard daily dosage. Kovarik also states that the daily dosage employed following a loading dose regimen can be 0.1 – 0.5 mg or can be much larger, e.g., 2.5 or 5.0 mg. Thus, Kovarik teaches that the daily dosage administered after the initial period can vary substantially relative to the standard daily dosage and is dependent on the immediately preceding loading dose administered during the initial phase. In addition to being only one of a wide range of dosages that can be employed following a loading dose regimen of an S1P receptor modulator or agonist, the 0.5 mg daily dosage referenced in Kovarik is mentioned only in the context of a dosage employed following the conclusion of a loading dose

regimen. In view of the above, Applicants submit that the skilled person reading Kovarik would attach no significance to the suitability of any daily dosage mentioned therein outside the context of an immediately preceding loading dose regimen. Put another way, Kovarik teaches such a broad daily dosage range that one skilled in the art would not arrive at the specific, claimed daily dose (0.5 mg), even if the skilled artisan followed Kovarik's loading dose regimen as taught. Therefore, Applicants respectfully contend that in the absence of a prior loading dose regimen, there is no way, without extensive and undue experimentation, that a skilled artisan would be able to arrive at the claimed daily dose with any expectation of success.

Applicants further submit that Virley does not provide the skilled person with any guidance regarding a favorable human dosage, *i.e.*, favorable with respect to the balance of safety and efficacy, to use in RRMS. They simply refer to the use of FTY720 to treat multiple sclerosis.

In view of the above, Applicants submit that all pending claims, as amended, comply fully with 35 U.S.C. §103, and they respectfully request that such claims be allowed to issue.

If the Examiner believes that a telephone conversation with Applicants' Attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at (862) 778-5816. The Director is hereby authorized to charge any fees required to Deposit Account No. **19-0134** in the name of Novartis.

Respectfully submitted,

/Andrew Holmes/

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/257,342	04/21/2014	Peter C. Hiestand	PAT050279-US-PCTD	7853

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EXAMINER
WEDDINGTON, KEVIN E

ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
04/06/2015	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No. 14/257,342	Applicant(s) HIESTAND ET AL.	
	Examiner KEVIN E. WEDDINGTON	Art Unit 1629	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *August 18, 2014*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1-6* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-6* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☒ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 12/303,765.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *4/21/2014; 8/18/2014; 12/17/2014*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

The present application is being examined under the pre-AIA first to invent provisions.

Claims 1-6 are presented for examination.

Applicants' preliminary amendment filed August 18, 2014; and the information disclosure statements filed April 21, 2014, August 18, 2014 and December 17, 2014 have been received and entered.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged.

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119 (a)-(d). The certified copy has been filed in parent Application No. 12/303,765, filed on 12/08/2008.

Claim Rejections - 35 USC § 103

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which

> said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under pre-AIA 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under pre-AIA 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of pre-AIA 35 U.S.C. 103(c) and potential pre-AIA 35 U.S.C. 102(e), (f) or (g) prior art under pre-AIA 35 U.S.C. 103(a).

Claims 1-6 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Virley, “Developing Therapeutics for the Treatment of Multiple Sclerosis”, The Journal of the American Society for Experimental NeuroTherapeutics, Vol. 2, pages 638-649 (October 2005) of PTO-1449 in view of WO 2006/058316, hereby known as Kovarik et al. of PTO-1449.

Virley teaches the administration of 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-propane-1,3-diol, also known as FTY720, which is a sphingosine-1-phosphate receptor modulator, for the treatment of multiple sclerosis (MS). Virley distinguishes between the categories of relapsing-remitting MS and primary progressive MS. See the introduction on page 638, as well as the discussion of experimental models for MS on page 640. Note page 640, first paragraph and second paragraph teaches the administration of the active agent at the point of relapse significantly suppressed further progression of clinical signs and providing compelling evidence for this agent as a potential therapeutic agent for MS. Date from a phase II clinical trial with FTY720, confirmed a relapse reduction rate of more than 50% in 281 relapsing-remitting MS patients for 6 months of treatment.

The instant invention differs from the cited reference in that the cited reference does not teach the preferred dosage of 0.5 mg. However, the secondary reference, Kovarik et al., teaches dosage regimens involving S1P receptor agonists, of which FTY720 is clearly encompassed. Note on page 17, line 16, a daily dose of 0.5 mg is disclosed for the treatment autoimmune diseases, of which MS is recited as an example (see page 14, lines 7-8).

Therefore, one skilled in the art would have been motivated to administer FTY720 with a reasonable expectation of success in reducing, preventing or alleviating relapses in relapsing-remitting multiple sclerosis and slow the progression of relapsing-remitting multiple sclerosis.

Claims 1-6 are not allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KEVIN E. WEDDINGTON whose telephone number is (571)272-0587. The examiner can normally be reached on 12:30 pm -9:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffery S. Lundgren can be reached on (571)272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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