CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209884Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	March 19, 2019
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 209884
Product Name and Strength:	Mayzent (siponimod) tablet, 0.25 mg and 2 mg
Applicant/Sponsor Name:	Novartis Pharmaceutical Corporation
FDA Received Date:	March 14, 2019
OSE RCM #:	2018-1287-2
DMEPA Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA Team Leader:	Briana Rider, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Neurology Products (DNP) requested that we review the revised starter pack labeling for Mayzent (siponimod) (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised starter pack blister card label is unacceptable from a medication error perspective.

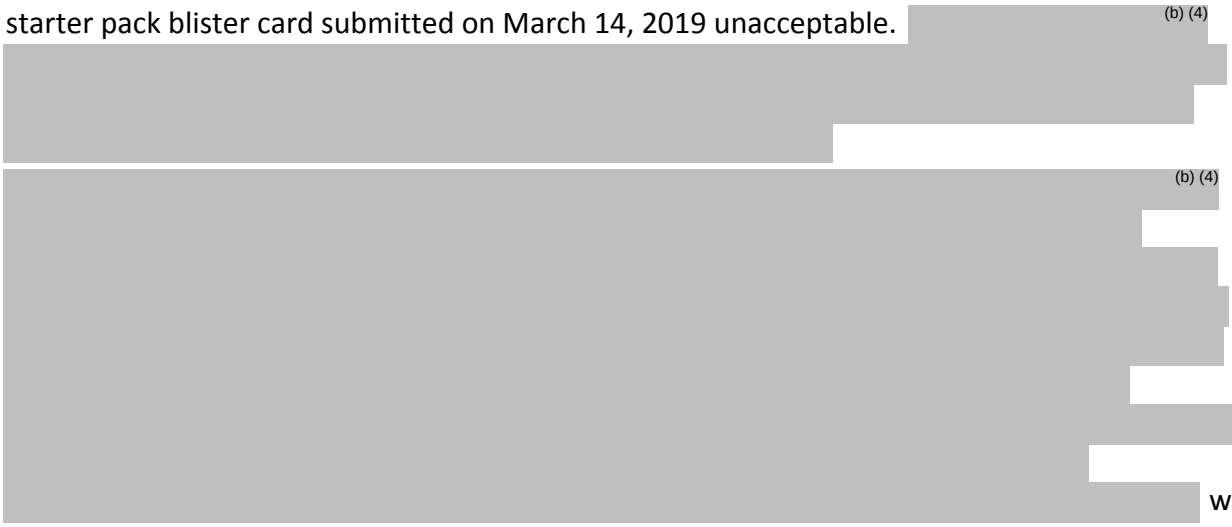
We disagree with the revisions proposed for the starter pack blister card label (and, subsequently, the proposed revisions to the Prescribing Information (PI) Section 2.2 and Section 2.3). (b) (4)

(b) (4)

[a] Morris, C. Label and Labeling Review MEMO for Mayzent (siponimod) NDA 209884). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAR 06. RCM No.: 2018-1287-1.

3 RECOMMENDATIONS FOR NOVARTIS

We find your proposed label and labeling revisions to the Prescribing Information (PI) and the starter pack blister card submitted on March 14, 2019 unacceptable.



we recommend use of the starter pack is limited to patients who will be prescribed a 2 mg daily maintenance dose. We also recommend the intended user is clearly identified on the starter pack labels, labeling, and within the PI.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON MARCH 14, 2019

Starter Pack Blister Card

Starter Pack Carton

Starter Pack Blister Sleeve

(b) (4)

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/s/

JOHN C MORRIS
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BRIANA B RIDER
03/19/2019 12:18:21 PM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Templates
Version: 2018-01-24

Date:	March 15, 2019
Reviewer:	Catherine Callahan, PhD, MA Division of Epidemiology I
Team Leader:	Kira Leishear, PhD, MS Division of Epidemiology I
Division Deputy Director:	Sukhminder K. Sandhu, PhD, MS, MPH Division of Epidemiology I
Subject:	ARIA Sufficiency Memo for Pregnancy Safety Concerns
Drug Name:	Mayzent (siponimod)
Application Type/Number:	NDA 209884
Submission Number:	Novartis
OSE RCM #:	2018-1286

1. BACKGROUND INFORMATION

1.1. Medical Product

Siponimod is a sphingosine-1-phosphate (S1P) receptor modulator with the proposed indication to treat secondary progressive multiple sclerosis (SPMS). Siponimod is administered orally. The proposed dose is 2mg daily after a five-day dose titration. The single maximum tolerated dose was determined to be 25mg based upon the occurrence of symptomatic bradycardia after single doses of 75mg. The proposed labeling includes warnings and precautions for increased risk of infections, macular edema, bradyarrhythmia, and decreased liver function.

Table 1. Increased Events of Interest in long-term safety pools[a]

Event, n (%)	Placebo n =607	Siponimod 2-10mg n= 1737
Infections	301 (49.6)	1004 (57.8)
Macular edema	1 (0.2)	26 (1.5)
Cardiac disorders	62 (10.2)	250 (14.4)
Hepatic Test Increased	24 (4.0)	255 (14.7)

[a]Sources: Summary of Siponimod summary of clinical safety in multiple sclerosis and 120-day clinical safety update, Novartis.

1.2. Describe the Safety Concern

Safety during pregnancy due to drug exposure is a concern for women who are pregnant or of childbearing potential. The potential risk/benefit profile of MS disease-modifying treatment during pregnancy is unclear, pregnancy may reduce the risk of MS relapse, but there may be an increased risk of relapse after delivery or when stopping MS treatment.[1] In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.[2]

The receptor affected by siponimod is known to be involved in vascular formation and skeletal development during embryogenesis in rodents. Siponimod was present in the fetus after oral administration to pregnant rats. Administration of siponimod to rats and rabbits during the period of organogenesis at levels greater than the maximum recommended human dose (MRHD) resulted in the following adverse effects:[3]

- Siponimod administered orally to rats during the period of organogenesis fetal resorption and teratogenicity (skeletal malformations, e.g., cleft palate and misshapen clavicles, cardiomegaly, and edema) were noted at doses greater than or equal to 1 mg/kg/day (19 times the MRHD).
- Siponimod administered orally to rabbits, resulted in a significant increase in embryo-fetal deaths and skeletal variations at doses greater than or equal to 1 mg/kg/day (2 times the MRHD) and abortions and increased skeletal or visceral variations at 5 mg/kg/day (10 times the MRHD).
- In a pre- and post-natal development study, pregnant rats received oral doses of siponimod up to 0.5 mg/kg/day during the period of organogenesis and until weaning. In the F0 generation dams, doses greater than or equal to 0.15 mg/kg/day resulted in effects on body weight and food consumption as well as in increased gestation length. At 0.5 mg/kg/day, the numbers of dead and malformed pups were increased.

- In F1 generation pups, adverse clinical signs, decreased body weight and decreased postnatal survival were observed at greater than or equal to 0.15 mg/kg/day. Increased abnormalities including external, urogenital and skeletal findings were observed greater than or equal to 0.15 mg/kg/day. In F1 generation adults, delayed sexual maturation, but no effects on reproductive function or behavioral performance were noted at 0.5 mg/kg/day.

There are no adequate and well-controlled studies that investigated adverse pregnancy outcomes after siponimod exposure and a lack of pregnancy studies generally. Siponimod has a half-life of about 30 hours. In the siponimod clinical studies, women who were pregnant were excluded and birth control during participation was required for women of reproductive potential. However, a total of 7 patients were exposed to siponimod after conception for approximately 22-78 days. Of the 7 patients with post-conception exposure, 3 patients delivered normal full-term infants; 3 patients had elective abortions (none because of a known defect); and one had a spontaneous abortion (gestational age not reported).[4,5] Overall, the data on pregnancy exposure during clinical trials are insufficient to inform the risk associated with siponimod.

In the current proposed labeling, as of March 15, 2019 the Risk Summary in Section 8.1 states:

8.1 Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with the use of MAYZENT in pregnant women. Based on animal data and its mechanism of action MAYZENT can cause fetal harm when administered to a pregnant woman *(see Data).* Reproductive and developmental studies in pregnant rats and rabbits have demonstrated MAYZENT induced embryo toxicity and fetotoxicity in rats and rabbits and teratogenicity in rats. Increased incidences of post-implantation loss and fetal abnormalities (external, urogenital and skeletal) in rat and of embryo-fetal deaths, abortions and fetal variations (skeletal and visceral) in rabbit were observed following prenatal exposure to siponimod starting at a dose 2 times the exposure in humans at the highest recommended dose of 2 mg/day.

In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Data

Animal Data

(b) (4)

(b) (4)

[redacted]

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	x

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected

☐ No approved indication, but practitioners may use product off-label in pregnant women

☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized

☒ No approved indication, but use in women of child bearing age is a general concern

2.2. Regulatory Goal

☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty

☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of

statistical precision and certainty. †

☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review). †

† ***If checked, please complete General ARIA Sufficiency Template.***

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☒ Pregnancy registry with internal comparison group
☐ Pregnancy registry with external comparison group
☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
☒ Electronic database study with chart review
☐ Electronic database study without chart review
☒ Other, please specify: alternative study designs would be considered: e.g., retrospective cohort study using claims or electronic medical record data or a case control study

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

☐ Study Population
☐ Exposures
☐ Outcomes
☐ Covariates
☒ Analytical Tools

For any checked boxes above, please describe briefly:

Analytical Tools: ARIA analytic tools are not sufficient to assess the regulatory question of interest because data mining methods have not been tested for birth defects and other pregnancy outcomes.

Because broad-based signal detection is not currently available, other parameters were not assessed.

2.5. Please include the proposed PMR language in the approval letter.

The Division of Neurology Products requests two PMRs related to pregnancy outcomes. As of March 15, 2019, the proposed PMR language for these are:

> Conduct prospective pregnancy exposure registry cohort analyses in the United States that compare the maternal, fetal, and infant outcomes of women with multiple sclerosis exposed to Mayzent during pregnancy with two unexposed control populations: one consisting of women with multiple sclerosis who have not been exposed to Mayzent before or during pregnancy and the other consisting of women without multiple

	sclerosis. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, preterm births, small for gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life. Conduct a pregnancy outcomes study using a different study design than provided for in PMR XXXX-X (for example, a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small-for-gestational-age births in women exposed to Mayzent during pregnancy compared to an unexposed control population.

3. References

1. Alroughani R, Altintas A, Al Jumah M, et al. Pregnancy and the Use of Disease-Modifying Therapies in Patients with Multiple Sclerosis: Benefits versus Risks. Multiple sclerosis international. 2016;2016:1034912.

2. Dinatale M. Division of Pediatric and Maternal Health, FDA. The pregnancy and lactation labeling rule (PLLR). https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM520454.pdf. Accessed October 11, 2018.

3. Novartis. Siponimod Toxicology Written Summary. January 15, 2018. DARRTS

4. Novartis. Summary of Clinical Safety in multiple sclerosis. February 28, 2018. DARRTS

5. Novartis. An Extension Study to the CBAF312A2201 study to evaluate long-term safety, tolerability and efficacy of BAF312 given orally once daily in patients with relapsing remitting multiple sclerosis. October 4, 2017. DARRTS

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/s/

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	March 13, 2019
To:	Billy Dunn, MD Director **Division of Neurology Products (DNP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Kelly Jackson, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Domenic D'Alessandro, PharmD, MBA, CDE Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	MAYZENT (siponimod)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 209884
Applicant:	Novartis Pharmaceutical Corporation

1 INTRODUCTION

On March 28, 2018, Novartis submitted for the Agency's review an original New Drug Application (NDA) 209884 for MAYZENT (siponimod) tablets, for oral use for the proposed indication: for the treatment of secondary progressive multiple sclerosis (SPMS) in adults.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology Products (DNP) on July 14, 2018 and September 17, 2018, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for MAYZENT (siponimod) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft MAYZENT (siponimod) MG received on March 28, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 4, 2019.
- Draft MAYZENT (siponimod) Prescribing Information (PI) received on March 28, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 4, 2019.
- Approved GILENYA (fingolimod) comparator labeling dated January 11, 2019.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: March 13, 2019

To: David E. Jones, M.D., Clinical Reviewer
Division of Neurology Products (DNP)

Nahleen Lopez, PharmD, Regulatory Project Manager, (DNP)

Tracy Peters, PharmD, Associate Director for Labeling, (DNP)

From: Domenic D'Alessandro, PharmD, MBA, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, RN, MPH, Team Leader, OPDP

Subject: OPDP Labeling Comments for MAYZENT™ (siponimod) tablets, for oral use

NDA: 209884

In response to DNP consult request dated September 17, 2018, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for the original NDA submission for MAYZENT™ (siponimod) tablets, for oral use.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DNP (Nahleen Lopez) on March 4, 2019, and are provided below.

Medication Guide: A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide were sent under separate cover on March 13, 2019.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on March 1, 2019, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Domenic D'Alessandro at (301) 796-3316 or domenic.dalessandro@fda.hhs.gov.

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	March 6, 2019
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 209884
Product Name and Strength:	Mayzent (siponimod) tablet, 0.25 mg and 2 mg
Applicant/Sponsor Name:	Novartis Pharmaceutical Corporation
FDA Received Date:	March 1, 2019
OSE RCM #:	2018-1287-1
DMEPA Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA Team Leader:	Lolita White, PharmD

1 PURPOSE OF MEMORANDUM

Division of Neurology Products (DNP) requested that we review the revised trade and sample container labels, and the starter pack carton, blister sleeve, and blister card for Mayzent (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

Additionally, the Division has finalized the dosing for this product, which provides for two titration regimens. As noted in our previous review, the 12 tablet (5 day) starter pack ends with a dose of 1.25 mg. However, the finalized titration regimen for patients intended to take a 1 mg maintenance dose will be different from the titration regimen for patients intended to take a 2 mg maintenance dose (Appendix B). Therefore, the starter pack is only appropriate for use in patients intended to take a maintenance dose of 2 mg.

2 CONCLUSION

We identified areas of the revised starter pack carton and blister sleeve where information can be added to help ensure the safe and effective use of this product. We provide

[a] Morris, C. Label and Labeling Review for Mayzent (siponimod) NDA 209884. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 FEB 05. RCM No.: 2018-1287.

recommendations below in Section 3 for Novartis to address our concerns. We advise these recommendations are implemented prior to the approval of this NDA.

3 RECOMMENDATIONS FOR NOVARTIS

The revised starter pack carton and blister sleeve labeling are unacceptable from a medication error perspective. (b) (4) We recommend the following be implemented prior to approval of this NDA:

- (b) (4) we recommend you add a warning statement prominently on the principle display panel of the starter pack carton and blister sleeve labeling. You may consider something similar to the following:
    - This titration pack is only intended for patients who will receive the 2 mg maintenance dosage

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APPENDIX B. DOSE TITRATION REGIMENS FOR MAYZENT

Table 1 Dose Titration Regimen to Reach MAYZENT 2 mg Maintenance Dosage

Titration	Titration Dose	Titration Regimen
Day 1	0.25 mg	1 x 0.25 mg
Day 2	0.25 mg	1 x 0.25 mg
Day 3	0.5 mg	2 x 0.25 mg
Day 4	0.75 mg	3 x 0.25 mg
Day 5	1.25 mg	5 x 0.25 mg

Table 2 Dose Titration Regimen to Reach MAYZENT 1 mg Maintenance Dosage

Titration	Titration Dose	Titration Regimen
Day 1	0.25 mg	1 x 0.25 mg
Day 2	0.25 mg	1 x 0.25 mg
Day 3	0.5 mg	2 x 0.25 mg
Day 4	0.75 mg	3 x 0.25 mg

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/s/

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Medical Officer's Review of NDA 209884
Ophthalmology Consult

NDA 209884	Submission Date	July 26, 2018
Consult Review	Review completed:	January 21, 2018

Product Name: Mayzent (siponimod)

Sponsor: Novartis

Requested: The Division is kindly requested to review the optical coherence tomography data submitted with the original NDA. Specifically, the optical coherence tomography (OCT) findings with respect to macular edema in the patient evaluations. The PDUFA date is March 26, 2019.

Reviewer's Comment: *While OCTs were performed on subjects in the clinical trials, the applicant did not collect the OCTs from the clinician's offices and therefore was not able to submit the OCTs when requested by the Agency. Some numerical values were collected from the OCT scans, but these values are not sufficient without the scans to verify the macular edema diagnoses. For the purposes of this review, the investigator's diagnosis of macular edema is taken at face value.*

Submitted:
In the controlled pool, macular edema (including cystoid macular edema) was reported as an Adverse Event (AE) in 20 (1.7%) siponimod 2 mg patients (Odds ratio of 10.7 vs Placebo 95% CI: 1.4, 80.3) and 1 (0.2%) placebo patient. One additional case (2.0%) was reported in the siponimod 10 mg dose group. Macular edema, confirmed by ophthalmologist assessment, was unilateral in most patients and associated with new visual impairment in 9 of the 20 patients in the siponimod 2 mg dose group.

Of the 20 patients on siponimod 2 mg with an AE of macular edema, 2 (10%) patients had a medical history of diabetes mellitus and uveitis (both known risk factors for macular edema) and in 3 patients (15%) macular edema was preceded by other events (increased intraocular pressure, retinal detachment and diabetes mellitus) indicating that patients with these risk factors may be more likely to develop macular edema on siponimod. There is no evidence of an increase in the incidence of macular edema over time with siponimod treatment and the reported cases in the Long-term pool were consistent with the observations in the Controlled pool. 25 patients (1.4%) [IR of 0.6 per 100 PY] had an AE of macular edema in the Long-term pools [SCS-Table 2-31]. This is four additional cases compared to the siponimod treated patients in the Controlled pool. Of the 4 patients, 2 had an onset of macular edema within the first 6 months, 1 patient around 12 months of commencing siponimod therapy and one occurred 24 months after commencing siponimod [SCS-Section 2.1.5.5].

Reviewer's Comment: *Disagree that the five patients' history of diabetes mellitus, uveitis, increased intraocular pressure, or retinal detachment contributed to the incidence of macular edema.*

Macular edema improved on discontinuing therapy. In 9 of the 12 patients who permanently discontinued siponimod 2 mg due to macular edema the event outcome was reported as recovered/ recovering, while for 3 of the 12 patients the reported outcome of the events was not recovered at the time of study phase

completion in study A2304. Nine patients recovered from the event following temporary interruption of siponimod. Four patients experienced recurrence of macular edema upon rechallenge with siponimod.

Onset of macular edema

Approximately 65% (13/20) of the events had an onset of macular edema within the first 4 months of commencing siponimod treatment. Based on ophthalmologist assessment, macular edema was present (unilateral in most patients) and associated with new visual impairment in 9 out of 20 patients taking siponimod during double-blind treatment (Table 12-15, Listing 16.2.9-9.3).

Table 12-15 shows the time to first occurrence of TEAEs of macular edema. A total of 13 of the 20 siponimod patients had the first TEAE of macular edema on or before Day 105, 4 of 20 between Day 105 and Day 365, and 3 of 20 beyond 1 year.

Table 12-15 Patients with TEAEs of macular edema as assessed by ophthalmologist during Core Part including open-label siponimod (SAF)

Patient	Onset day [a]	End day [a,b]	Action with study drug	Affected eye	Visual impairment	Outcome
(b) (6)	17	After	Permanently discontinued	Both	No	Not recovered at end of Core Part
	29	66	Permanently discontinued	Left	Yes	Recovered
	29	232	Permanently discontinued	Right	Yes	Recovered with sequelae
	652	After	Patient had already Discontinued	Right	No	Recovered
	29	approx. 120	Permanently Discontinued	Left	Yes	Recovered
	84	148	Temporarily interrupted and never restarted	Both	No	Recovered
	213	253	No action	Left	No	Recovered
	338	After	No action	Left	No	Not recovered at end of Core Part
	85	119	Permanently discontinued	Right	No	Recovered
	87	143	Temporarily interrupted	Left	No	Recovered
	90	169	Permanently Discontinued	Right	No	Recovered
	90	After	Permanently Discontinued	Left	Yes	Not recovered at end of Core Part
	92	127	Temporarily interrupted	Right	Yes	Recovered
	93	121	Permanently discontinued	Left	No	Recovered

	150	186	Patient had already discontinued	Left	No	Recovered
(b) (6)	99	127	Temporarily Interrupted	Right	No	Recovered
	250	302	Permanently Discontinued	Both	No	Recovered
	105	317	Temporarily interrupted	Right	No	Recovered
	360	After	Permanently discontinued	Right	Yes	Recovering
	139	181	Temporarily interrupted	Right	No	Recovered
	322	386	Temporarily interrupted	Right	Yes	Recovered
	377	After	Permanently Discontinued	Both	Yes	Not recovered at end of Core Part
	278	345	Temporarily Interrupted	Left	No	Recovered
	358	After	Permanently discontinued	Left	Yes	Recovering
	540 (106 days after Open Label Switch	706	Temporarily interrupted	Both	No	Recovered
	664	706	Permanently discontinued	Both	No	Recovered
	543	625	Temporarily Interrupted	Left	No	Recovered
	566	After	Permanently discontinued	Left	Yes	Recovering
	649	After	Patient had already discontinued	Right	No	Not recovered at end of Core Part
	708	After	Temporarily interrupted	Right	No	Not recovered at end of Core Part

[a] Study day is relative to the reference start date.
[b] If at end of treatment or post-treatment follow-up epochs, the end date is missing: “After” is displayed.

Reviewer's Comment: *The onset of four cases of macular edema occurred in the first month of treatment. The onset of the majority of cases of macular edema occurred between months 1 and 4.*

Labeling Comments

Reviewer's Comment: *It is recommended that the labeling of the package insert related to ocular adverse reactions be revised as described below:*

Highlights:

- Macular Edema: An ophthalmic evaluation is recommended if there is any change in vision while taking Mayzent. (5.2)

Warnings:

5.2 Macular Edema

(b) (4)

An ophthalmic evaluation is recommended if there is any change in vision while taking MAYZENT with an evaluation of the fundus, including the macula.

Continuation of Mayzent therapy in patients with macular edema has not been evaluated. A decision on whether or not Mayzent should be discontinued needs to take into account the potential benefits and risks for the individual patient.

(b) (4)

*Grouping of preferred terms (PTs) were considered for ADR frequency determination

17 PATIENT COUNSELING INFORMATION

Macular Edema

Advise patients that Mayzent may cause macular edema and that they should contact their physician if they experience any changes in their vision while taking Mayzent.

MEDICATION GUIDE

What is the most important information I should know about Mayzent?

Mayzent may cause serious side effects, including:

(b) (4)

...

- Problem with your vision (Macular edema)

...

What should I tell my healthcare provider before taking Mayzent?

...

•

...

What are the possible side effects of Mayzent?

Mayzent may cause serious side effects, including:

...

(b) (4)

...

Summary Conclusions: There is no objection from an ophthalmology prospective to the approval of MAYZENT with the labeling recommendations described in this review.

Wiley A. Chambers, M.D.
Supervisory Medical Officer, Ophthalmology

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/s/

WILEY A CHAMBERS
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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	February 5, 2019
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 209884
Product Name and Strength:	Mayzent (siponimod) tablet, 0.25 mg and 2 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Novartis Pharmaceuticals Corporation
FDA Received Date:	June 28, 2018
OSE RCM #:	2018-1287
DMEPA Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA Team Leader:	Lolita White, PharmD

1 REASON FOR REVIEW

The Division of Neurology Products (DNP) requested we review the proposed Prescribing Information (PI), Medication Guide (MG), trade container labels, carton, blister sleeve, blister card labeling and professional sample container labels for Mayzent (siponimod) for areas of vulnerability that may increase the risk for medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C (N/A)
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of the proposed Prescribing Information (PI), Medication Guide (MG), trade and sample container labels, and the trade carton, blister sleeve, and blister card identified the following areas that can be improved to decrease risk of medication error and to align with Federal Regulations:

Prescribing Information (PI)

- Section 16 of the full PI and Medication Guide
    - The refrigeration storage statement “Store between 2C - 8C” contains the “-“ symbol, which is inconsistent between the carton labeling, container label and remainder of the PI.

All labels (Trade and Professional Sample)

- The strength presentation can be improved to increase readability.

Trade and professional sample container labels and titration pack carton

- The format for the expiration date is not defined, which may lead to confusion and deteriorated drug medication errors.

Trade and professional sample container labels and titration pack carton and blister card sleeve

- The refrigeration storage statement is not prominent, which may lead to deteriorated drug medication errors.
- The refrigeration storage statement "Store between 2-8°C" contains the "-" symbol, and is missing the unit of measure "C" after the number 2, which may contribute to deteriorated drug medication errors.

Trade and professional sample container labels

- The after dispensing storage statement " may be stored at 20 to 25°C" does not contain the unit of measure "C" after each numeric digit, which is inconsistent and may contribute to deteriorated drug medication errors.

Trade and professional sample container labels for 2 mg strength only

- The presentation of the strength for the 2 mg tablets is not prominent.

Titration pack blister card sleeve

- The placement and the intended format for the lot number and expiration date are not identified per 21 CFR 201.10(i)(1) and per 21 CFR 201.17.

We provide recommendations in Sections 4.1 and 4.2 to address these concerns and to reduce the risk for medication errors with the use of the product.

We note the carton labeling and container labels describe the dosage form as "tablet" in the strength statement and as "(b) (4) tablet" in the net quantity statement. We defer to the Office of Pharmaceutical Quality (OPQ) to address the acceptability of this presentation.

We also note the 12 tablet (5 day) starter pack ends with a dose of 1.25 mg; (b) (4) We provide a review of the titration pack labeling from a medication error perspective, however we defer to the Division to address the acceptability of this dosing regimen.

4 CONCLUSION & RECOMMENDATIONS

We identified areas of the proposed labels and labeling where information can be improved or added to help ensure the safe and effective use of this product We provide recommendations below in section 4.1 for the division and in section 4.2 for the Sponsor to address our concerns. We advise these recommendations are implemented prior to the approval of this NDA.

4.1 RECOMMENDATIONS FOR THE DIVISION

- Section 16 of the Full PI and Medication Guide
    - The refrigeration storage statement "Store between 2C - 8C" contains the "-" symbol. To decrease risk of misinterpretation and to ensure consistency

between the carton labeling and container labels and PI, the symbol should be replaced with its intended meaning. We recommend the statement "Store between 2°C-8°C" be revised to read "Store between 2°C to 8°C"

4.2 RECOMMENDATIONS FOR NOVARTIS PHARMACEUTICALS CORPORATION

We recommend the following be implemented prior to approval of this NDA:

- All labels (Trade and Professional Sample)
  - As currently presented, the strength statement is not presented with space between numerical dose and unit of measure. To improve readability, we recommend you place adequate space between the numerical dose and unit of measure (e.g. 0.25 mg instead of 0.25mg).
- Trade and professional sample container labels and titration pack carton
  - As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
- Trade and professional sample container labels and titration pack carton and blister card sleeve
  - As currently presented, the refrigeration storage statement is not prominent, which may increase the risk for deteriorated drug medication errors. We recommend you revise and bold the statement (b) (4) to read "Must be refrigerated, store at 2°C to 8°C (36°F to 46°F)."
  - As currently presented, the refrigeration storage statement (b) (4) contains the "-" symbol and is missing the unit of measure "C" after the number 2. To decrease risk of misinterpretation and to decrease risk of deteriorated drug medication error, we recommend you revise the statement (b) (4)
- Trade and professional sample container labels.
  - As currently presented, the post-dispensing storage statement "(b) (4) at 20° to 25°C" does not contain the unit of measure "C" after each numeric digit. To decrease risk of deteriorated drug medication errors and to ensure consistency throughout the labeling and labels, we recommend you revise the statement "(b) (4) at 20° to 25°C" to read "(b) (4) at 20°C to 25°C".
- Trade and professional sample container labels for 2 mg strength only

- As currently presented, [redacted] (b) (4) the color boxing used to highlight the strength [redacted] (b) (4), which decreases the prominence of the strength. We recommend you revise the color scheme so the strength appears [redacted] (b) (4) In addition, to increase prominence of the strength statement, ensure that the color used to highlight the 2 mg strength statement does not overlap with other colors utilized in the tradedress or with the green color utilized to highlight the 0.25 mg strength statement.

- Titration pack blister card sleeve
  - As currently presented, placement and intended format for the lot number and expiration date are not present. Add the lot number statement per 21 CFR 201.10(i)(1). Add the expiration date per 21 CFR 201.17.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Mayzent received on June 28, 2018 from Novartis Pharmaceuticals Corporation.

Table 2. Relevant Product Information for Mayzent	
Initial Approval Date	N/A
Active Ingredient	siponimod
Indication	Treatment of patients with secondary progressive multiple sclerosis (SPMS)
Route of Administration	Oral
Dosage Form	tablet
Strength	0.25 mg and 2 mg
Dose and Frequency	5 day titration Days 1 and 2: 0.25 mg Day 3: 0.5 mg Day 4: 0.75 mg Day 5: 1.25 mg Maintenance dose: 2 mg once daily Maintenance dosing in patients with CYP2C9 *1*3 or *2*3 genotype: 1 mg once daily
How Supplied	0.25 mg tablets Titration Pack containing 12 tablets (5 day supply) Bottle containing 28 tablets (7 day supply) 2 mg tablets Bottle containing 30 tablets (30 day supply)
Storage	Prior to dispensing: Refrigerate between 2°C to 8°C (36°F to 46°F). After dispensing to patient: Titration Pack: Store at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature] for up to 1 week after dispensing. The Titration Pack calendarized blister wallet should be stored in its original wallet container.

	Bottles: Stored at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature] for up to 1 month after dispensing.
Container Closure	HDPE bottles with (b) (4) closures Heat-sealed, foil-backed, (b) (4) blister card containing 12 tablets

APPENDIX B. PREVIOUS DMEPA REVIEWS

On November 27, 2018, we searched for previous DMEPA reviews relevant to this current review using the terms, siponimod, Mayzent, and BAF312. Our search did not identify any previous reviews.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Mayzent labels and labeling submitted on June 28, 2018 by Novartis Pharmaceuticals Corporation.

- Trade container labels
- Professional and sample container labels
- Trade Titration Pack carton, blister sleeve, and blister card labeling
- Medication Guide (image not shown)
- Prescribing Information (Image not shown)

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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M E M O R A N D U M

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: February 4, 2019

To: Billy Dunn, MD, Director
Division of Neurology Products

Through: Dominic Chiapperino, PhD, Director
Martin Rusinowitz, MD, Senior Medical Officer
Silvia Calderon, PhD, Senior Pharmacologist
Controlled Substance Staff

From: Jovita Randall-Thompson, PhD, Pharmacologist
Controlled Substance Staff

Subject: **NDA 209884**
Generic Name (Trade Name): siponimod (Mayzent)
Dosages: 0.25, 0.5, 0.75, and 1.25 mg titration dose once a day up to a maintenance dose of 2 mg
Formulations, route: 0.25 and 2 mg film-coated tablets, oral
IND: 76122
Indication(s): Secondary progressive multiple sclerosis (SPMS)
Sponsor: Novartis Pharmaceuticals Co.
PDUFA Goal Date: March 26, 2019

Materials Reviewed:

- NDA 209884, eCTD 0000, 0001, 0002, submitted March 28, 2018, April 27, 2018, June 8, 2018
- BAF312 (siponimod) Abuse Potential Assessment, submitted March 28, 2018
- BAF312: Drug Discrimination Abuse Liability Testing in Rat, submitted March 28, 2018, Report 1270591
- BAF312: Assessment of Potential Self-Administration in Male and Female Rats, submitted March 28, 2018, Report 1270590
- BAF312: Investigation of the Potential to Induce Physical Dependency in the Rat following 4 Weeks of Oral Administration, submitted March 28, 2018, Report 1570351
- BAF312: NVP-BAF312: In vitro Safety Pharmacology Profile, Report RD-2006-50780
- Phase 1 Study Reports A2101, A1101, A2119, A2104, A2111, A2108, A2124, A2128, A2126, A2122, A2129, A2102, A2105, A2107, A2110, A2118, A2121, and A2125
- Phase 2 Study Reports A2201, A2202, A2205, and A2206
- Phase 3 Study Report A2304

Table of Contents

I. SUMMARY

1. Background

This memorandum responds to a consult request dated July 4, 2018 from the Division of Neurology Products (DNP) regarding siponimod, trade name Mayzent (NDA 209884 and IND 76122). Siponimod is a sphingosine 1-phosphate receptor modulator under development by Novartis Pharmaceuticals Co. (Sponsor). It is a new molecular entity (NME) to be used as a disease modifying treatment for patients with secondary progressive multiple sclerosis (SPMS), given at a recommended maintenance dose of 2 mg orally, taken once daily.

Siponimod is a central nervous system (CNS) active drug with its primary mode of action as an agonist at the sphingosine-1-phosphate subtype 1 (S1P1) receptor. It is also selective for the S1P subtype 5 (S1P5) receptor. Functionally, siponimod causes the internalization of the S1P1 receptor and thus it functions as an antagonist when modulating S1P1.

In terms of abuse, siponimod binds to receptors (e.g. dopamine, serotonin, and opiate-mu, -delta and -kappa) that are associated with abuse-related effects, and its use is associated with central nervous system (CNS)-mediated adverse events (AEs, e.g., abnormal behavior, somnolence, and disturbance in attention.

Based on its pharmacology and siponimod's potentially abuse -related AEs, CSS recommended that the Sponsor conduct nonclinical abuse potential studies (CSS review, Lerner, Alicja, October 29, 2015, DARRTS). In response, the Sponsor submitted nonclinical drug discrimination, self-administration, and dependence and withdrawal protocols and studies (CSS review, Lerner, Alicja, May 6, 2016, DARRTS; CSS review, Randall-Thompson, Jovita, November 2, 2017, DARRTS). After reviewing preliminary data submitted by the Sponsor, CSS concluded that a human abuse potential (HAP) study was not necessary for siponimod's NDA submission (CSS review, Randall-Thompson, Jovita, November 2, 2017, DARRTS).

Siponimod is not a scheduled substance under the Controlled Substances Act (CSA). Its mechanism of action is similar to fingolimod (Gilenya, NDA 022527), a S1P-modulator with high affinity for S1P1, S1P3, S1P4, and S1P5. Fingolimod is not a controlled substance.

2. Conclusions

1. The Sponsor states that siponimod is not chemically or pharmacologically similar to any known drug of abuse, does not produce psychoactive effects that are abuse related, and thus has no abuse potential and is unlikely to be abused. Upon assessment of the pharmacology, chemistry, and the absence of abuse-related adverse events reports in clinical trials, CSS agrees with the Sponsor and concludes that siponimod does not meet criteria to be scheduled under the Controlled Substance Act (CSA).

2. Siponimod's mechanism of action is similar to that of fingolimod (Gilenya, NDA 22527); however, siponimod is a selective agonist at S1P1 and S1P5 receptors.

3. Binding assays demonstrate that at high concentrations (higher than 10 micromolar) siponimod selectively binds to several receptors associated with abuse, including opioid receptors. The Sponsor did not conduct functional assays to address the agonist or antagonist activity of siponimod at receptors systems activated or blocked by drugs with abuse potential. However, due to the high levels of plasma-bound siponimod (greater than 99.9%) it is not expected that significant concentrations of siponimod will reach the brain to activate these receptors. This is confirmed by the lack of CNS effects of siponimod in animals, and by the lack of abuse-related adverse events (AEs) in clinical trials in healthy subjects and patients with multiple sclerosis.

4. In the nonclinical abuse and dependence studies conducted with siponimod, there weren't any abuse signals found (i.e., no generalization to a scheduled drug, no difference in self-administration responding compared to placebo, and no differences in withdrawal-related behavior compared to placebo).

5. Abuse-related AEs were not reported in clinical trials. CSS conducted a review of the AEs collected during Phase 1, 2 and 3 studies and reviewed the abuse-related AE assessment conducted by the Sponsor. When siponimod was administered to healthy volunteers in Phase 1 studies there were no potentially abuse-related AEs. The observed CNS-associated AEs were non-specific and included headache, dizziness, and somnolence. These are not consistent with those typically associated with abuse (i.e., sedation, euphoric, or elevated mood). Nonspecific CNS AEs were also reported in MS patients, however most of these were not clearly abuse-related.

3. Recommendations

Based on the lack of an abuse signal found with siponimod, CSS recommends no Section 9, Drug Abuse and Dependence in the siponimod label (Of note, the label for fingolimod, also a S1P-modulator, does not include a Section 9, Drug Abuse and Dependence.)

II. DISCUSSION

Siponimod is an NME being developed as a disease modifying treatment for patients with secondary progressive multiple sclerosis (SPMS). The pathophysiology of MS is appearing to involve the activation of autoimmune lymphocytes outside of the CNS, with subsequent egress into the CNS after activation. Siponomod is an oral sphingosine-1- phosphate (S1P) modulator whose mechanism of action presumably relates to its ability to bind to S1P receptors on various lymphocytes, preventing their movement out of lymphoid tissue into the peripheral circulation and thereby into the CNS with a resulting decrease in inflammatory response.

Since siponimod is selective for S1P1 (and S1P5), it may have the potential for efficacy in auto-immune disorders like MS with less S1P3-mediated side effects such as AV block resulting in bradyarrhythmias as well as possible QTc prolongation.

1. Chemistry

1.1 Drug Substance

Siponimod's chemical properties:

- chemical name is (S)-N-((2S,3R)-1-Amino-3-hydroxy-1-oxobutan-2-yl)-1-((S)-1-((2S,3R)-2-amino-3-hydroxybutanoyl)pyrrolidine-2-carbonyl) pyrrolidine-2-carboxamide
- molecular formula is $C_{18}H_{31}N_5O_6$
- molecular weight is 413.47 g/mol
- CAS # 1230487-00-9

1.2 Drug Product and Recommended Dosing

Siponimod is supplied as a 0.25 mg round biconvex film-coated immediate release tablet and a 2 mg round biconvex film-coated tablets. The proposed use of siponimod states that treatment should be initiated with a 5-day oral (PO) dose of 0.25 mg of siponimod taken once on Days 1 and 2, followed by once daily doses of 0.5 mg on Day 3 (two tablets of 0.25 mg), 0.75 mg on Day 4 (three tablets of 0.25 mg), 1.25 mg of siponimod on Day 5 (five tablets of 0.25 mg), reaching the maintenance dose of 2 mg once a day starting on Day 6.

2. Nonclinical Pharmacology

Time to peak plasma siponimod concentrations (T_{max}) following PO dosing in most animal species is 7 to 8 hours. In the rat, a sex difference in pharmacokinetics (PK) was observed. Clearance is faster in males than females. Siponimod is cleared from the systemic circulation with a half-life ($T_{1/2}$) of approximately 5 hours in male rats and 29 hours in female rats.

When taken orally, the bioavailability of siponimod is approximately 50% and 71% in rat and monkey, respectively. Also, when comparing rats to monkeys, absorption in cynomolgus monkey is faster at lower doses (T_{max} of 2.5 hours) and a longer $T_{1/2}$ is observed in the monkey (and mouse), approximately 19 hours dosing.

When compared to humans, the mean/median T_{max} is relatively late for rodent species (7 to 8 hours post-dose) after PO administration. However, the mean $T_{1/2}$ is similar between humans (approximately 30 hours; range ~27 to 57 hours) compared with other animal species, other than the male rat ($T_{1/2}$ of approximately 5 to 6 hours, see Sponsor's table shown below, Table 1).

Table 1: Summary of siponimod pharmacokinetic parameters across species

	Rat	Mice	Monkey	Human
Tmax (h) (p.o.)	7 – 8	8	2.5 - 7	4 (2 – 6)
T1/2 (h) (p.o.)	5 – 6 [a)]	27	16	~ 30 (27 – 57)
CL [L/h/kg] (i.v.)	0.36 - 0.53 [b)]	-	0.098	3.11 - 3.15
Vss [L/kg] (i.v.)	2.2 – 3	-	2.12	1.77
Plasma protein binding / Fraction unbound (F_u)	> 99.9% / 0.0003	> 99.9% / 0.0001	> 99.9% / 0.0003	> 99.9% / 0.0002

a) In male rats. In female rats, $T_{1/2}$ was ~ 29 h.

b) In male rats. In female rats, CL was 0.074 L/h/kg.

Source: Reports DMPK R1300411-02, DMPK R0500017-02, DMPK R0900164-01, DMPK R1600437, RD-2005-00583], DMPK R1000166-01, DMPK R0400881-01, and DMPK R1300902-01 (Source: Abuse Potential Assessment, submitted March 28, 2018, page 39.)

2.1 Receptor Binding and Functional Assays

The Sponsor conducted a receptor screening of off-target receptors (approximately 98 receptors, at 10 μM). As seen in Table 2, data from the screening revealed that siponimod also binds (>50% binding inhibition at ≤10 μM concentrations) to the opiate-mu, -delta and -kappa receptors, the dopamine 1 (D_1), D_2, D_3, and D_5 receptors, the serotonin 1A ($5\text{-}HT_{1A}$), $5\text{-}HT_{2A}$, $5\text{-}HT_{2B}$, and $5\text{-}HT_{2C}$ receptors, the histamine-1 (H_1) and H_2 receptor, the dopamine transporter (DAT), norepinephrine transporter (NET), and serotonin transporter (SERT), and the sodium channel, site 2 (Report RD-2006-50780).

Table 2: Percent of binding inhibition of siponimod

Percent of binding inhibition of siponimod in human brain cortex and rat brain cerebellum cells, 5 batches of siponimod were tested (highest binding inhibition percent is displayed)		
	Human	Rat
hr Adenosine 3 (Ad_3) receptor	90	--
*hr Adrenergic Alpha 2A ($alpha_{2A}$) receptor	100	--
*hr Adrenergic Alpha 2B ($alpha_{2B}$) receptor	98	--
*hr Adrenergic Alpha 2C ($alpha_{2C}$) receptor	81	---
hr Angiotensin I (AT_1) receptor	82	---
hr Angiotensin II (AT_2) receptor	78	---
*hr Dopamine 1 (D_1) receptor	89	---
*hr Dopamine 2 (D_2) receptor (long form)	75	---
*hr Dopamine 3 (D_3) receptor	90	---
*hr Dopamine 5 (D_5) receptor	62	---
*hr Dopamine transporter (DAT)	95	---
h Epidermal growth factor (EFG)	67	---
h Estrogen (ERα) receptor	60	---

hr Muscarinic (M_5) receptor	60	---
*hr Histamine (H_1) receptor	88	---
hr Histamine (H_2) receptor	100	---
*h Serotonin 1A (5-HT_{1A}) receptor	59	---
*hr Serotonin 2A (5-HT_{2A}) receptor	98	---
*hr Serotonin 2B (5-HT_{2B}) receptor	77	---
*hr Serotonin 2C (5-HT_{2C}) receptor	59	---
*hr Norepinephrine transporter (NET)	85	---
*h Opiate mu receptor	95	---
*hr Opiate delta receptor	70	---
*hr Opiate kappa receptor	55	---
*hr Serotonin Transporter (SERT)	72	---
*r Na channel type II	---	88
*r Testosterone	---	62
Source: Report RD-2006-50780 tissue type: r=rat, h=human, hr human recombinant, rr=rat recombinant; *Abuse-related receptors		

Functional assays were not conducted. However, as indicated by the Sponsor, it is unlikely that siponimod will reach brain concentrations high enough to interact with these receptors. Siponimod is highly bound to plasma proteins (> 99.9%) and there would be limited amounts of unbound siponomod available to reach the brain. For example, the concentrations of siponimod at the therapeutic dose of 2 mg (and 10 mg, 5 times the therapeutic dose) are estimated to be present in the cerebrospinal fluid (CSF) (presumed surrogate for brain concentrations) several thousand-fold lower than the receptor binding IC50 values for any of the off-target sites.

The primary metabolites of siponimod include NVP-LYS815 (M17), NVP-LYG778 (M16), and NVP-LNL925 (M3). M17 and M16 were evaluated for off-target activity on 56 targets (32 GPCRs, 5 transporters, 4 ion channels, 6 nuclear receptors and 9 enzymes) and M3 was evaluated on 29 targets (12 GPCRs, 3 transporters, 3 ion channels, 3 nuclear receptors and 8 enzymes), which are potentially involved in suicidality. The study was not conducted to evaluate targets associated with abuse. However, several of the targets (receptors) that were assessed in this study, are also known to be linked

to abuse-related effects. The only activity found was in the 5-HT_{2A} antagonist assay (Report RD-2016-00166, RD-2016-00167, and RD-2016-00545). Base on the results siponimod metabolites do not appear to bind at relevant levels to receptors that are associated with abuse-related effects and therefore are not likely to induce such effects.

The receptor binding findings for siponimod are similar to the marketed drug fingolimod, which also has significant affinities to off-target CNS/abuse-related receptors (Ad_3, $Alpha_{2A}$, $Alpha_{2B}$, $Alpha_{2C}$, beta-1 adrenergic [$Beta_1$], cannabinoid type 1 [CB_1], D_1, D_3, D_5, H_1, H_2, H_3, motilin, M_5, neurotensin 1 [NT_1], Opiate-kappa, Opiate-mu, 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, DAT, and NET). It is also present in low concentrations in CSF due to high protein binding (99.7%; Gilenya® CDS 2017[1]). Also, fingolimod has not been shown to be associated with abuse, dependence or diversion (BAF312 Abuse Potential Assessment, March 28, 2018, pages 97 - 103)[2].

2.2 Safety Pharmacology/Metabolites

Following PO administration of siponimod to humans, M3 (hydroxylation followed by glucuronidation) and the cholesterol ester M17 were the major circulating metabolites (27% to 39% and 81% to 97% of parent, respectively). Both metabolites amounted to greater than 10% of the total drug related exposure. Howevert, M16 is not detected in humans. The M3 and M17 metabolites did not bind to off-target receptors at relevant concentrations (all IC50 values ≥ 9.6 μM [9600 nM], where 0.59 nM and 0.066 nM are the estimated CSF concentrations of M3 and M17, respectively, at steady state following a supratherapeutic siponimod dose of 10 mg/day, i.e., > 16000-fold). Therefore, the M3 and M17 human metabolites are not thought to contribute to the pharmacological activity of siponimod in humans.

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[1] Gilenya® CDS (2017), Novartis Pharmaceuticals. Gilenya ™ (fingolimod) 0.25mg and 0.5mg hard capsules. Core Data Sheet (CDS); Version 3.2. 07-Nov 2017.

[2] The Sponsor conducted searches for reports of abuse-related signals with fingolimod (Gilenya®) using publicly available post-marketing sources, including World Health Organization (WHO) VigiBase, FDA Adverse Event Reporting System (FAERS), National Poison Data System (NPDS), Drug Abuse Warning Network (DAWN, for the year 2011), scientific literature (Pubmed, up to January 2018), and Internet forums (Erowid Experience Vaults, Bluelight, and Drug Form; up to January 2018). Most searches covered a period of up to February 2017, no signals of abuse, misuse, diversion, dependence or withdrawal with fingolimod were identified.

2.3 Findings from Safety Pharmacology and Toxicology Studies

In single-dose toxicity studies conducted in rats, mice, and monkeys that were administered siponimod at a dose range of 10 -2000 mg/kg orally (gavage) or IV produced the following clinical behavioral signs:

- Mice (male & female):
  - no clinical signs

(siponimod at 0, 50, 100, 150, or 200 mg/kg (IV), Report 0670303)

- Rats (male & female):
  - at 2000 mg/kg, included poor grooming, abnormal gait and stance (only in females)

(siponimod at 0, 250, 500, 1000 or 2000 mg/kg (PO), Report 0670304; and siponimoid at 0, 100, or 200 mg/kg, Report 0670302)

- Monkeys (male):
  - no clinical signs

(siponimod at 10, 30, or 60 mg/kg (PO), Report 0470204)

In repeated-dose, 2 - 104-week oral (gavage) and 2-week IV toxicity studies conducted in rats, mice, and monkeys that were administered siponimod, at a dose range of 5 - 300 mg/kg/day produced the following clinical behavioral signs:

- Mice (male & female):
  - at doses ≥ 2 mg/kg/day (PO) given for 104 weeks - hunched posture decreased activity, and tremors
  - at 150 mg/kg/day (PO) -trembling and decreased motor activity (only in males)
  - at 300 mg/kg/day (PO) -reduced muscle tone, trembling, decreased motor activity, hunched posture, pale appearance, and recumbency (only in males)

(siponimod at 0, 50, 150, or 300 mg/kg/day (PO), Report 0770648; siponimod at 0, 5, 15, 35, or 80 mg/kg/day (PO), Report 0770649; and siponimoid at 0, 2, 8, or 25 mg/kg/day (PO), Report 0870139)

The no-observed adverse effect level (NOAEL) was not assessed in mice.

- Rats (male & female):
  - ≥ 24 mg/kg/day -reduced activity
  - ≥ 36 mg/kg/day (IV) - subdued and sluggish and semi-closed eyes (only in males)
  - 120 mg/kg/day - subdued and sluggish (only in males)
  - 200 mg/kg/day -vocalization, hypersensitivity to touch, severe incoordination and/or abnormal gait

(siponimod at 0, 12, 36, or 120 mg/kg/day (IV) for males, and 0, 4, 12, or 24 mg/kg/day (IV) for females with a 4 Week Treatment-free Period, Report 8355783; siponimod at 15, 50 or 150 mg/kg/day (PO) for males, and 5, 15 or 50 mg/kg/day (PO) for females with a 8-week recovery period, Report 0770059; siponimod at 0, 10, 30, or 100 mg/kg/day (PO), Report 0410113; and siponimod at 10, 50 or 200 mg/kg/day (PO) with 4-week recovery period, Report 0670037)

For rats the NOAEL was considered to be 12 mg/kg/day (IV; C_{max} of 1020 and 3770 ng/mL for males and females respectively) and 10 mg/kg/day (PO) (see plasma and brain concentrations below in the Sponsor's tables, Table 3, 4, and 5). All clinical signs were resolved after during recovery periods.

Table 3: Toxicokinetic parameters of BAF312 in rat plasma after single dose

Treatment	Parameter	Units	Male	Female
10 mg/kg/day	Tmax	Hours	3	6
	Cmax	ng/mL	1410	2700
	Cmax/Dose	ng/mL/mg/kg/day	141	270
	$AUC_{(0\text{-}24h)}$	ng*Hours/mL	19500	52100
	$AUC_{(0\text{-}24h)}$/Dose	ng*Hours/mL/mg/kg/day	1950	5210
50 mg/kg/day	Tmax	Hours	3	3
	Cmax	ng/mL	6360	12100
	Cmax/Dose	ng/mL/mg/kg/day	127	242
	$AUC_{(0\text{-}24h)}$	ng*Hours/mL	93300	204000
	$AUC_{(0\text{-}24h)}$/Dose	ng*Hours/mL/mg/kg/day	1870	4070
200 mg/kg/day	Tmax	Hours	3	3
	Cmax	ng/mL	9430	18300
	Cmax/Dose	ng/mL/mg/kg/day	47.2	91.5
	$AUC_{(0\text{-}24h)}$	ng*Hours/mL	134000	367000
	$AUC_{(0\text{-}24h)}$/Dose	ng*Hours/mL/mg/kg/day	672	1830

(Source: Report 0670037, page 381)

Table 4: Toxicokinetic parameters of BAF312 in rat plasma after multiple dose

Treatment (mg/kg/day) / duration	Parameter	Units	Male	Female
10	Tmax	Hours	3	3
29 days	Cmax	ng/mL	1900	5670
	Cmax/Dose	ng/mL/mg/kg/day	190	567
	$AUC_{(0-24h)}$	ng*Hours/mL	21700	107000
	$AUC_{(0-24h)}$/Dose	ng*Hours/mL/mg/kg/day	2170	10700
50	Tmax	Hours	3	3
29 days	Cmax	ng/mL	6640	21500
	Cmax/Dose	ng/mL/mg/kg/day	133	430
	$AUC_{(0-24h)}$	ng*Hours/mL	86300	404000
	$AUC_{(0-24h)}$/Dose	ng*Hours/mL/mg/kg/day	1730	8080
200/100*	Tmax	Hours	6	3
29 days*	Cmax	ng/mL	21600	30200
	Cmax/Dose	ng/mL/mg/kg/day	108	302
	$AUC_{(0-24h)}$	ng*Hours/mL	365000	603000
	$AUC_{(0-24h)}$/Dose	ng*Hours/mL/mg/kg/day	1830	6030

* Daily dosing of females was reduced to 100 mg/kg/day at day 13. After 2 days washout period (day 11 and day 12)

(Source: Report 0670037, page 383)

Table 5: BAF312 concentration in brain homogenate tissue at necropsy

Dose (mg/kg/day)	Subject	Gender	(ng/g)
0	1016M	Male	0.00
0	1516F	Female	0.00
10	2011M	Male	1900
10	2012M	Male	1500
10	2013M	Male	1190
10	2511F	Female	16300
10	2512F	Female	20100
10	2513F	Female	15100
50	3011M	Male	6600
50	3012M	Male	6380

50	3013M	Male	6330
50	3511F	Female	84000
50	3512F	Female	70800
50	3513F	Female	96800
200	4016M	Male	52700
200	4017M	Male	38900
200	4018M	Male	43000
100	4516F	Female	188000
100	4517F	Female	163000
100	4518F	Female	190000

(Source: Report 0670037, page 391)

- Monkeys (male & female):
  - at 100 mg/kg/day (PO) -hypersensitivity and tremors/convulsions
  - at 200 decreased to150 mg/kg/day (PO) -clonic convulsions, salivation, muscle tremors, ataxia, decreased locomotor activity or recumbency, vocalization, twitching, hypersensitivity to touch

(0, 10, 50, and 200 decreased to 150 mg/kg/day (PO) with 4-week recovery period, Reports 0670007, 10, 50 and 100 mg/kg/day (PO) with a 12-week recovery period, Report 0770061; 0, 30, or 100 mg/kg/day (PO) with a 8-week recovery period, Report 0770339 and 10, 30, and 100 mg/kg/day (PO), Report 0570040)

For monkeys the NOAEL was determined to be 10 mg/kg/day (PO; plasma and brain concentrations in Table X and X) for 4 weeks and more and 30 mg/kg/day (PO) for 2 weeks and all clinical signs were resolved after during recovery periods. Mean toxicokinetic values at doses 10, 30 and 100 are presented below in the Sponsor's tables, Table 6 and 7).

Table 6: Mean toxicokinetic parameters of BAF312 in monkey plasma

Dose	Study day	Gender	Tmax	Cmax	SD	Cmax/ dose	AUC	SD	AUC/ dose	n
10	1	Male	4.50	4040	628	404	67400	9160	6740	4
		Female	4.50	3200	685	320	51900	20000	5190	4
	28	Male	4.50	5110	1090	511	92500	22600	9250	4
		Female	6.00	5800	2630	580	101000	54400	10100	4

	154	Male	4.50	5250	717	525	94000	8790	9400	4
		Female	4.50	5910	3190	591	106000	63100	10600	4
	357	Male	4.50	5440	785	544	95400	16600	9540	4
		Female	3.75	6620	3170	662	124000	80900	12400	4
30	1	Male	5.25	11000	772	365	198000	5450	6580	4
		Female	4.50	9380	1810	313	157000	32300	5220	4
	28	Male	4.50	19200	1490	639	351000	53200	11700	4
		Female	5.25	13900	2470	462	242000	53700	8040	4
	154	Male	5.25	23800	5700	792	427000	100000	14200	4
		Female	5.25	16100	2870	536	278000	88700	9260	4
	357	Male	5.25	18000	2960	600	331000	54000	11000	4
		Female	6.00	12100	3130	403	215000	54200	7160	4
100	1	Male	6.00	19100	5640	191	339000	89200	3390	6
		Female	6.00	16800	4760	168	293000	76800	2930	6
	28	Male	5.00	41900	16400	419	786000	323000	7860	6
		Female	5.50	40600	11700	406	761000	244000	7610	6
	154	Male	4.80	53300	32300	533	1020000	628000	10200	5
		Female	6.00	40200	10600	402	750000	212000	7500	6
	357	Male	6.00	46000	20300	460	884000	387000	8840	4
		Female	6.00	31000	8560	310	565000	170000	5650	6

Units: dose [mg/kg/day], T_{max} [hours], C_{max} [ng/mL], C_{max}/dose [(ng/mL)/(mg/kg/day)], AUC [ng*Hours/mL], AUC interval [0-24 Hours], AUC/dose [(ng*Hours/mL)/(mg/kg/day)]. (Source: Report 0770339, page 2390)

Table 7: Mean BAF312 concentrations (ng/g) and % CV in monkey brain

Dose	Study day	Gender	Mean	% CV	n 10	366
	Male	24200	8.3	4		
		Female	29500	78	4	
30	366	Male	84200	16.9	4	
		Female	54000	44.1	4	
100	208†	Male	200000	n.c.	1	
	366	Male	237000	n.c.	2	
		Female	170000	14.1	4	
	396‡	Male	2380	n.c.	1	

421	Male	1900	n.c.	1
	Female	1520	n.c.	2
Ratio day 421 / 366	Male	0.0080		
	Female	0.0089		

Unit: dose [mg/kg/day]. † The animal 4002M died on day 208. ‡ The animal 4006M died on day 396. n.c., not calculable. (Source: Report 0770339, page 2389)

2.4 Animal Behavioral Studies

According to the Sponsor, female rats have higher (3 to 5 fold) systemic exposure of BAF312 than male rats. The Sponsor proposed to exclusively use female rats as subjects in both preclinical abuse assessments. However, testing both male and female animals was recommended since abuse-related sex differences can be independent of the systemic exposure levels of the test drug within each sex (see Lerner, CSS review, 5/6/2016).

Drug Discrimination: Report 1270591

For drug discrimination, oral administration of siponimod at doses 0.3, 1, 50, and 150 mg/kg were given to male Lister Hooded rats, and 0.15, 0.5, 10, and 50 mg/kg were given to female rats. did not generalize to the discriminative properties of midazolam (5 mg/kg in males, 1.25 mg/kg in females, oral administration), or amphetamine (0.3 mg/kg, subcutaneous injection). Siponimod concentrations at 4.5 hours post-dose ranged from 22 to 7435 ng/mL in males at 0.16 and 150 mg/kg, and from 8 to 10985 ng/mL in females at 0.04 and 50 mg/kg, respectively. This is acceptable.

The methods used in this study are acceptable. The training dose for midazolam and amphetamine fell within the full generalization criteria of more than 80% correct responses on their associated levers. Siponimod did not impair the performance of animals in terms of lever pressing ability. Oral administration of 0.3, 1.0, 50, and 150 mg/kg siponimod (males) or 0.15, 0.5, 10, and 50 mg/kg siponimod (females) did not generalize to midazolam, with a group mean of ≤ 20% midazolam associated lever responding at all doses. Also, oral administration of 0.3, 1.0, 50, and 150 mg/kg siponimod (males) or 0.15, 0.5, 10, and 50 mg/kg siponimod (females) did not generalize to amphetamine, with a group mean of ≤ 20% amphetamine associated lever responding at all doses. Based on these findings the drug does not share the discriminative cue of amphetamine or midazolam.

Self-administration: Report 1270590

For self-administration, under a fixed-ratio 10 (FR10), schedule substitution of 0.01, 0.04, and 0.5 mg/kg/infusion siponimod for cocaine (0.32 mg/kg/infusion) were evaluated in male and female Lister Hooded rat. Dose selection for siponimod (0.01 to 0.4 mg/kg/infusion) covered C_{max} values from 31 to 1980 ng/mL after single bolus administrations (single dose mean C_{max} of 15.4 ng/mL at a therapeutic dose of 2 mg, and 77.3 ng/mL at 10 mg in humans). This is acceptable.

The methods used in this study are acceptable. According to the Sponsor the low dose (0.01 mg/kg/infusion) was approximately equal to the human exposure of 0.4 ng/ml. Siponimod exposed rats had a different pattern of responding in comparison to that reported with cocaine. Also, the siponimod response pattern was comparable to the response pattern response reported with vehicle. The group mean number of rewards for the combined siponimod substitution sessions was comparable across all doses (0.01, 0.05, and 0.4 mg/kg/infusion) with that of the vehicle substitution. The response over the 5-day substitution period had an extinction-like pattern (excluding Day 1, rewards decreased from 16 to 6) instead of an increase as is typically shown with reinforcement behavior. These findings indicate that siponimod is not self-administered by animals, and we may conclude that it will not function as a positive reinforce.

2.5 Tolerance and Physical Dependence Studies in Animals

Physical dependence: Report 1570351

Oral administration of siponimod at 0.3, 1, 50, and 150 mg/kg/day to male rats, and 0.15, 0.5, 10, and 50 mg/kg/day to female rats for 28 days did not produce withdrawal symptoms upon cessation of dosing comparable to the withdrawal symptoms reported with diazepam (30 mg/kg/day). Siponimod's mean plasma levels in rats were reported at higher levels than the human exposure plasma level of 30.4 ng/ml following 25 days of oral administration. For male rats: 63, 168, 3808, and 9640 ng/ml were reported at doses of 0.3, 1, 50, and 150 mg/kg/day, respectively; and for female rats: 67, 160, 3973, and 13583 ng/ml at doses 0.15, 0.5, 10 and 50 mg/kg/day, respectively were reported.

The methods used in this study are acceptable. Siponimod group mean plasma levels prior to the withdrawal phase (Day 25, 4.5 hours post dose) were 63, 168, 3808 and 9640 ng/mL (0.3, 1, 50 and 150 mg/kg/day, respectively) for male rats and 67, 160, 3973 and 13583 ng/mL (0.15, 0.5, 10 and 50

mg/kg/day) for female rats. Based on these findings we conclude that chronic exposure to siponimod will not result in physical dependence.

3. Clinical Pharmacology

Siponimod is a new member of a class of oral compounds referred to as sphingosine-1-phosphate (S1P) receptor modulators. Siponimod has immunomodulatory and neuroprotective properties.

The absolute bioavailability of siponimod (tablet) as a single 0.25-mg dose administered orally was 84%. Siponimod pharmacokinetics after administration of a single oral dose is measurable in the plasma as early as 0.25 hours post dose and plasma concentration peaked between 3 and 6 hours (median), with an apparent terminal $T_{1/2}$ between 27 and 57 hours. Following multiple once daily dose administration of siponimod (0.3 to 20 mg), over 28 days, steady state was reached for all subjects after approximately 6 days. The mean accumulation ratio was between 1.88 and 2.72 on Day 28. The effective $T_{1/2}$ (based on drug accumulation at steady state) ranged between 22 and 36 hours. The comparison of PK parameters, including plasma protein binding percentages for siponimod is provided in the Sponor's table below, Table 8.

Table 8: Summary of siponimod pharmacokinetic parameters across species

	Rat	**Mice**	**Monkey**	**Human**
Tmax (h) (p.o.)	7 – 8	8	2.5 - 7	4 (2 – 6)
T1/2 (h) (p.o.)	5 – 6 a)	27	16	~ 30 (27 – 57)
CL [L/h/kg] (i.v.)	0.36 - 0.53 b)	-	0.098	3.11 - 3.15
Vss [L/kg] (i.v.)	2.2 – 3	-	2.12	1.77
Plasma protein binding / Fraction	> 99.9% / 0.0003	> 99.9% / 0.0001	> 99.9% / 0.0003	> 99.9% / 0.0002

a) In male rats. In female rats, $T_{1/2}$ was ~ 29 h.

b) In male rats. In female rats, CL was 0.074 L/h/kg.

(Source: BAF312 (siponimod) Abuse Potential Assessment, page 39)

3.1 Drug/Product Interactions

Other than a slight delay in T_{max}, food intake had no effect on the systemic exposure (C_{max}, AUC) to siponimod (Report A2111; tablet 0.25- and 4-mg doses). In Report A2111 the T_{max} was slightly delayed with food intake, 6 to 7 hours across both 0.25 mg and 4-mg doses, versus 4 hours.

4. Clinical Studies

A total of 25 clinical studies of siponimod have been completed: 20 clinical pharmacology studies in healthy subjects (18) or special populations (2). As of May 31, 2017, a total of approximately 3278 subjects have been enrolled. Healthy subjects have received siponimod as single doses (0.1 to 75 mg) or multiple doses (0.25 to 20 mg) daily up to 38 days.

Table 9: Studies Included in this Review

Study ID	Phase	Design	Subjects	Drug dose range	Population	Single or multiple dose	Age/Sex
A2101	Phase 1 ascending dose study	double-blind	98	2.5 - 75 mg or placebo	Healthy	single	18 to 55 years/M&F
A1101	Phase 1 ascending dose study	double-blind	40	0.5 - 10 mg or placebo	healthy-Japanese	single	20 to 45 years/M
A2119	Phase 1 compare different formulations	double-blind	60	4 mg or placebo	Healthy	single	18 to 55 years/M&F
A2104	Phase 1 ADME study	open-label	4	10 mg	Healthy	single	20 to 55 years/M
A2111	Phase 1 bioequivalence study	open-label	62	0.25 or 4 mg	Healthy	single	18 to 50 years/M&F
A2108	Phase 1 drug-drug interaction with fluconazole	open-label	14	4 mg	Healthy	single	18 to 55 years/M
A2124	Phase 1 drug-drug interaction with itraconozole	open-label	30	0.25 mg	Healthy	single	18 to 50 years/M&F
A2128	Phase 1 CYP2C9 extensive and poor metabolizers	open-label	24	0.5 or 0.25 mg	Healthy	single	18 to 70 years/M&F

A2126	Phase 1 IV study	open-label	33	0.25 mg	Healthy	single	18 to 50 years/M&F
A2122	Phase 1 pharmacokinetic studies	open-label	40	0.25 mg	Healthy	single	18 to 70 years/M&F
A2129	Phase 1 pharmacokinetic studies	open-label	40	0.25 mg	Healthy	single	18 to 70 years/M&F
A2102	Phase 1 multiple ascending dose study	double-blind	60	0.3, 1, 2.5, 10, or 20 mg, or placebo	Healthy	multiple	18 to 55 years/M&F
A2105	Phase 1 ascending dose study	double-blind	50	0.3, 1, 2.5, 10, or 20 mg, or placebo	Healthy	multiple	18 to 55 years/M&F
A2107	Phase 1 titration/cardiovascular tolerability study	double-blind	56	0.25 - 10 mg, or placebo	Healthy	multiple	18 to 64 years/M
A2110	Phase 1 treatment interruption and re-initiation /cardiovascular tolerability study, drug (discontinuation periods)	double-blind	122	0.5, 10, 20, or 40 mg, or placebo	Healthy	multiple	18 to 55 years/M&F
A2118	Phase 1 QT study (with moxifloxacin)	double-blind	304	2, or 10 mg, or placebo	Healthy	multiple	18 to 45 years/M&F
A2116	Phase 1 drug-drug interaction study with the beta blocker propranolol	double-blind	76	dose titration to 2 mg	Healthy	multiple	18 to 55 years/M&F
A2130	Phase 1 interrupted treatment pharmacodynamic study, vaccination challenge	double-blind	136	0.25, 0.5, 1, or 2 mg, or placebo	Healthy	multiple	18 to 55 years/M&F

A2121	Phase 1 oral contraceptive drug-drug interaction study	open-label	24	dose titration to 2 mg, or 4 mg	Healthy	multiple	18 to 40 years/F
A2125	Phase 1 drug-drug interaction study with rifampin	open-label	16	dose titration to 2 mg	Healthy	multiple	18 to 43 years/M&F
A2201	Phase 2 adaptive dose-ranging study evaluating safety, tolerability & efficacy; dose response curve	double-blind	297	0.25, 0.5, 1.25, 2, or 10 mg, or placebo	patients with relapsing remitting multiple sclerosis (RRMS)	multiple	18 to 55 years/M&F
A2202	Phase 2 proof of concept study to evaluate the efficacy and tolerability	double-blind followed by open-label with extended treatment	18	10 mg/day or 2 mg with 10 mg/day, or placebo	patients with polymyositis & dermatomyositis	multiple	18 to 75 years/M&F
A2205	Phase 2 proof of concept study to evaluate the efficacy and tolerability	double-blind followed by open-label with extended treatment	14	10 mg/day or 2 mg with 10 mg/day, or placebo	patients with polymyositis & dermatomyositis	multiple	18 to 75 years/M&F
A2206	Phase 2 safety, tolerability, efficacy and preliminary dose-response study	double-blind followed by open-label with extended treatment	17	0.5, 2, 10 mg, or placebo	patients with polymyositis & dermatomyositis	multiple	18 to 75 years/M&F
A2304	Phase 3 variable treatment duration study	double-blind followed by open-label with extended treatment	1651	titrated to 1 or 2 mg/day, & placebo tested	patients with secondary progressive multiple sclerosis (SPMS)	multiple	18 to 60 years/M&F

4.1 Adverse Event Profile

In the clinical studies conducted by the Sponsor, there were no clear abuse-related AEs associated with the use of siponimod. There was one case of feeling abnormal when the drug was given IV. There were numerous CNS-related AEs, including dizziness, fatigue, somnolence, lethargy, asthenia, irritability, depression, disturbance in attention, cognitive disorder, and paraesthesia reported by healthy subjects related to the study drug. None of these are considered abuse-related.

Patients with multiple sclerosis, polymyositis, and dermatomyositis had the following CNS-related AEs: intentional overdose, accidental overdose, suicide attempt, suicidal ideation, suicidal behavior, dizziness, fatigue, somnolence, completed suicide, impatience, hypoaesthesia, abnormal behavior, anxiety, affect lability, nervousness, agitation, irritability, restlessness, lethargy, asthenia, depression, panic attack, mood swings, mood altered, nightmare, delirium, mania, psychotic disorder, disturbance in attention, sensory disturbance, disorientation, cognitive disorder, abnormal dreams, and paraesthesia. Many of these were felt to be related to the study drug, although confounded their underlying MS and because a majority of patients took one or more concomitant medications. The most commonly used concomitant medications overall were analgesics and corticosteroids, primarily administered during an MS relapse.

Overdose and protocol deviations related to siponimod during Phase 2 and Phase 3 clinical trials were primarily related to medication errors (e.g., taking 2 tablets instead of 1 on one or more occasions), were observed in both siponimod and placebo groups, and were not considered to be related to abuse, diversion or drug-seeking behavior. There was one case of an intentional overdose in a Phase2 trial that was related to a suicide attempt.

For both healthy subjects and MS patients, the majority of CNS-related AEs were mild in severity. Eight MS patients reported potentially abuse-related AEs, including feeling abnormal, derealization, hallucinations and euphoric mood). In these patients it was not possible to determine whether or not these were due to siponomid, concomitant drugs, or their underlying MS. These AEs are shown in Table 4 and detailed in Table 5. Since there were no potentially abuse-related AEs in normal healthy subjects, it appears unlikely that siponimod caused these AEs in MS patients.

Table 10: Phase 2 and 3 Studies Single and Multiple doses

Phase 2 and 3 Studies Single and Multiple doses							
	Siponimod						
Adverse Event PT	PBO N=627	0.25 mg N=51	0.5 mg & dose titration to 0.5 mg	1.25 mg N=42	2 mg & dose titrations to 2 mg	10 mg dose titration to 10 mg	Drug Overall (N=1333)
Euphoria	0	0	0	0	0	0	0
Euphoric mood	0	0	0	0	1	1	2
Elevated mood	0	0	0	0	0	0	0
Mood alteration	0	0	0	0	0	0	0
Feeling drunk	0	0	0	0	1	0	1
Feeling abnormal	0	0	0	0	0	1	1
Mood elevation	0	0	0	0	0	0	0
Sedation	0	0	0	0	0	0	0
Psychotomimetic events	0	0	0	0	0	0	0
Hallucination (auditory/ visual)	0	0	0	0	2	0	2
Drug Maladministration	0	0	0	0	0	0	0
Derealization	0	1	0	0	1	0	2
Other relevant events	0	0	0	0	0	0	0
	*Source: Studies A2201, A2202, A2205, A2206, and A2304						

Table 11: Details of Potentially Abuse-Related AEs

Details of Potentially Abuse-Related AEs in Phase 2 and 3 Studies:

Subject identification number	Drug (dose)	Duration of AE	Narrative	PI Assessment	Severity	Outcome
ID_Not provided (Feeling abnormal)	0.25 mg, single IV infusion given over 3 hours	Not provided	Not provided	Not provided	Mild	Not provided
ID (b) (6) (Derealization)	0.25mg capsules taken once daily	1 day	35-year-old female Detailed narrative not provided.		Mild	Recovered/ resolved
ID (b) (6) (Feeling drunk)	2 mg capsules taken once daily	2 days	47-year-old male Detailed narrative not provided.	Not provided	Mild	Recovered/ resolved
ID_ (b) (6) (Hallucination)	Titrations from 0.25 to 2 mg, all capsules taken once daily.	15 days	50-year-old female On Day 51 (b) (6) the patient had symptoms of hallucination, psychosis, disorientation, and changed behaviors. On the next day (b) (6) (b) (6) treatment with study medication was permanently discontinued due to the events (psychotic disorder, hallucination). On (b) (6) the patient was hospitalized due to psychotic disorder and hallucination. On an unspecified date, an MRI of the brain did not show any new findings. The patient's treatment included quetiapine fumarate and clonazepam. The events (psychotic disorder, hallucination) were considered resolved on (b) (6) (b) (6) On (b) (6) the patient was discharged from the hospital. (Study A230, page 14687) Concomitant medications included baclofen for spasticity.	The Investigator did not suspect a relationship between the events (psychotic disorder, hallucination) and the study medication.	Serious	Recovered/ resolved
ID (b) (6) (Hallucination)	Titrations from 0.25 to 2 mg, all capsules taken once daily.	26 days	46-year-old female	Not associated with siponimod use.	Mild	Recovered/ resolved

ID (b) (6) (Feeling abnormal)		Titrations from 2 mg t0 10 mg, all capsules taken once daily.		271 days	59-year-old male Other medication or therapies were taken.	Not associated with siponimod use.	Mild	Recovered/ resolved
ID (b) (6) (Derealization)		0.25mg capsules taken once daily		30 days	51-year-old male	Not associated with siponimod use.	Moderate	Recovered/ resolved
ID_ (b) (6) (Euphoric mood)		Titrations from 0.25 to 2 mg, all capsules taken once daily	,	Not provided	58-year-old female On Day 299 (b) (6) the patient experienced worsening of depressive symptoms. The patient continued receiving treatment with fluoxetine for this event. On Day 343 (b) (6) the patient had mania and euphoric mood with elative symptoms. On the same day (b) (6) the patient was hospitalized and underwent a psychiatric evaluation. The Investigator reported that the patient had a history of depressive symptoms (since the age of 20) which led to a phase of hypomanic symptoms. The patient was treated with valproate sodium, olanzapine, lorazepam, haloperidol, and topiramate for these events. On Day 343 (b) (6) the treatment with study medication was permanently discontinued due to the	The Investigator suspected a relationship between the event (mania) and the study medication The Investigator did not suspect a relationship between the events (depressive symptoms, euphoric mood) and the study medication.	Life-threatening	Permanently discontinued

					event (mania) with last dose of study medication taken on Day 342 (b) (6) (b) (6) The events (depressive symptom, mania, euphoric mood) were not resolved at the time of last reporting (Study A2304, page 14812). Concomitant medications included fosfomycin, clavulanic acid and amoxicillin for urinary infection, baclofen for spasms due to MS, alprazolam and amantadine hydrochloride for anxiety due to MS, methylprednisolone for MS relapse, calcitriol for fatigue due to MS, fluoxetine for depression.			
ID_ (b) (6) (Euphoric mood)		Titrations from 2 mg t0 10 mg, all capsules taken once daily.		120 days	59-year-old male	Not associated with siponimod use.	Mild	Recovering/ resolving

4.2 Evidence of Abuse, Misuse, and Diversion

There were no issues of diversion, and no drug accountability issues. Phase 3 study dropouts or those discontinued from study analysis is shown in Table 6. There were no cases of study discontinuation due to abuse.

Table 12: Phase 3 population study discontinuations/drop-outs

Phase 3 population study discontinuations/drop-outs*(treatment with double-blind study drug, abbreviated visit schedule and treatment with open-label study drug)				
	Siponimod		**PLACEBO**	
	N = 1105	**(%)**	**N=546**	**(%)**
TOTAL DISCONTINUED	202	18.3	122	81.5
Discontinued due to AEs	45	4.1	18	3.3
Lack of Efficacy	16	1.4	11	2.0
Lost to Follow-up	9	0.8	8	1.5
Discontinued due to Physician Decision	13	1.2	1	0.2
Discontinued due Pregnancy	0	0	0	0
Protocol Violation	3	0.3	1	0.2
Withdrawal by Subject	96	8.7	77	14.1
Source: Study A2304				

4.3 Tolerance and Physical Dependence Studies in Humans

There were no signals of tolerance or dependence in animals. A human dependence/withdrawal study was not done.

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SILVIA N CALDERON
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Clinical Inspection Summary

Date	1 February 2019
From	Cheryl Grandinetti, Pharm.D., Reviewer Kassa Ayalew, M.D., M.P.H. Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Nahleen Lopez, R.P.M. Paul Lee, MD, Clinical Reviewer David Jones, MD, Clinical Reviewer Billy Dunn, M.D., Division Director Division of Neurology Products
NDA #	209884
Applicant	Novartis Pharmaceuticals Corporation
Drug	Mayzent (siponimod)
NME	Yes
Review Priority	Priority
Proposed Indication	Treatment of secondary progressive multiple sclerosis
Consultation Request Date	11 September 2018
Summary Goal Date	7 February 2019
Action Goal Date	7 January 2019
PDUFA Date	26 March 2019

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Hodgkinson, Maida, and Mao-Draayer, and the sponsor, Novartis Pharmaceuticals Corporation were inspected in support of this NDA. During the sponsor inspection, significant data reliability concerns were identified. The inspectional findings demonstrate that the blinding for Protocol BAF312A2304 was not adequately maintained as specified in the protocol throughout the course of the trial at 62 (21%) of 294 sites. Study personnel were given inappropriate access to the first dose and main databases affecting 285 (17%) out of 1651 total study subjects. The two databases contained information that could potentially unblind study personnel to the subjects' treatment assignment. Tracking database user activities, such as who and when users accessed the databases and what data were viewed, was limited because of the lack of system access audit trails to the first dose and main databases.

It is difficult to know if the inappropriate access to the information in these databases led to

the introduction of bias as database users may have viewed and used the information during the course of the trial. One, therefore, cannot rule out the introduction of bias during the study impacting the reliability of the study data, specifically for 163 of the 285 subjects who had study assessments performed by main database users and EDSS raters (i.e., blinded study personnel) who were granted inappropriate access to the first dose and/or main databases.

We recommended in an email, dated 19 December 2018, that the review division conduct a sensitivity analysis, excluding in the per-protocol analysis, the following subjects who may have been impacted:

- 62 subjects who were potentially affected by the 11 EDSS raters who had inappropriate access to the first dose or main databases
- 101 subjects who were potentially affected by the 32 users of the main database who had inappropriate access to the first dose database

The final compliance classification of the inspections of Drs. Hodgkinson and Mao Draayer was No Action Indicated (NAI). The final classification of the inspection of Dr. Maida was Voluntary Action Indicated (VAI) and the preliminary classification of the sponsor, Novartis Pharmaceuticals Corporation was Official Action Indicated (OAI). An inspection summary addendum will be generated if the preliminary classification of the sponsor changes.

II. BACKGROUND

Novartis Pharmaceuticals Corporation submitted this NDA to support the use of Mayzent (siponimod) for treatment of subjects with secondary progressive multiple sclerosis (SPMS). The key study supporting this application was the following protocol:

> BAF312A2304, "A multicenter, randomized, double-blind, parallel-group, placebo-controlled variable treatment duration study evaluating the efficacy and safety of Siponimod (BAF312) in patients with secondary progressive multiple sclerosis followed by extended treatment with open-label BAF312."

Subjects: 2092 subjects were screened, 1651 subjects were randomized

Sites: 294 sites in 31 countries

Study Initiation and Completion Dates: 20 December 2012 to 29 April 2016 (reflects the completion of the Core Part of the study; the extension part of the study is ongoing)

This was a multicenter, randomized, double-blind, parallel-group, placebo-controlled, variable treatment duration study that compared the efficacy and safety of siponimod to placebo in subjects with SPMS. The primary objective was to demonstrate the efficacy of siponimod compared to placebo in delaying the time to 3-month confirmed disability progression in subjects with SPMS as measured by the Expanded Disability Status Score (EDSS). The study design consisted of a Core Part followed by an open label Extension

Part.

The Core Part consisted of a Screening Epoch and a Treatment Epoch (starting on Day 1). During the Treatment Epoch, eligible subjects were randomized via an Interactive Response Technology (IRT) (in a 2:1 ratio) to one of two treatment arms:

- Siponimod 2mg taken orally once daily
- Matching placebo taken orally once daily

All subjects in the Core Part started treatment with a 6-day dose titration pack and were titrated up from 0.25 mg/day on day 1 to a 2 mg/day siponimod/matching placebo dose on day 6. Thereafter, if the subject's absolute peripheral lymphocyte count (APLC), measured at scheduled clinic visits, was less than 0.2 x109/L for two assessments, taken one week apart, the subject underwent a blinded dose reduction to siponimod/matching placebo dose 1 mg/day. In the Treatment Epoch, the treatment duration was based on when the study-stop criteria were met (treatment duration range was 23 to 42 months).

The primary efficacy endpoint was the time to 3-month confirmed disability progression, defined as the time from the start of study medication to the onset of disability progression (confirmed after an additional 3 months) as measured by EDSS. The EDSS was assessed, based on neurological examination, by an Independent EDSS Rater every 3 months and in the case of a suspected MS relapse. During the study, EDSS scores were recorded using both paper and electronic methods.

Early phase 1 studies detected dose dependent bradyarrhythmic effects within 2-3 hours after intake of first dose of siponimod. Slowly up-titrating siponimod during the first days of treatment effectively mitigated first dose bradyarrhythmic effects. Thus, first dose monitoring procedures were required for all subjects in the first half of the study. First dose monitoring procedures were relaxed after 5 May 2014 and required only for subjects who were considered to have potential risk factors for AV conduction slowing or other pre-defined cardiovascular risk factors (i.e., subjects who met the expanded cardiovascular status criteria as defined in the protocol).

Because of first dose bradyarrhythmic effects of siponimod (which could potentially unblind the treatment assignment), Novartis implemented use of the following:

- Unblinded first dose administrators/ restricted first dose teams to complete first dose assessments (e.g., vital signs, ECG assessments, mobile cardiac telemetry/Holter monitoring)
- A first dose electronic case report form (eCRF)/EDC system for first dose administrators to enter their first dose assessments

In addition, independent EDSS raters were required per the protocol to be blinded to the study treatment and not to be involved in any aspect of the subject's care and/or management of the MS treatment. Moreover, the EDSS raters were to remain blinded to adverse events, concomitant meds, lab data, and any other data that have the potential to

reveal the treatment assignment.

To maintain and support the integrity of the blind, the protocol used the following three electronic data capture (EDC) systems:

- Oracle's Remote Data Capture (RDC) system for the First Dose database (also referred to as BAF312A2304B or B database) -- this system contained subject information, labs and other test results which if viewed could potentially unblind study personnel to the treatment assignment. "Unblinded" first dose administrators, the first dose teams, and Novartis first dose monitors were supposed to access and use the First Dose database. The main study teams at each site, EDSS Raters and blinded Novartis CRA should not have had access to this system.

- Oracle's RDC system for the Main database (also referred to as BAF312A2304 database or main database) -- this system contained all other study information, except the EDSS scores and ePRO data. Note that near the end of the trial, EDSS scores were entered into this system because the vendor who provided the central NESC system went out of business. All blinded study personnel used this system.

- Central NESC system – this system contained the EDSS scores/raw data from the EDSS raters

In the Clinical Study Report, Amendment 1, dated 19 July 2018, Novartis provided information related to inappropriate access to the first dose and main databases by Novartis personnel and the study teams at the sites who were blinded to the study data (i.e., main study teams that used the main database and EDSS raters who used the Central NESC system). Novartis captured protocol deviations for inappropriate database access under the following protocol deviation codes:

- GCP01: "Not following per protocol blinding procedures but integrity of the study is not compromised." These were protocol deviations for dual database access by the Primary Treating Physician/Team (i.e., main database users who had inappropriate access to the first dose database)
- GCP01B: "Blinding procedures not followed in the first dose database."
- GCP10: "Dual database access by members of the first dose team but integrity of the study is not compromised." These were protocol deviations for dual database access by the First Dose Administrator/Team (i.e., first dose database users who had inappropriate access to the main database).
- PROC47: EDSS raters who had access to the first dose or main database.

We further investigated these protocol deviations that identified inappropriate database access to the first dose and main databases and the impact these protocol deviations had on the integrity of the study blind during the clinical investigators and the sponsor inspections.

Rationale for Site Selection

The clinical sites were chosen primarily based on numbers of enrolled subjects, treatment effect, protocol deviations for blinding and inappropriate database access, and prior inspectional history.

III. RESULTS (by site):

Site / Name of CI/ Address	Protocol # / # of Subjects Enrolled	Inspection Dates	Classification
Site 1023 **Suzanne Hodgkinson, MD** Level L1, Mental Health Building, Cnr Goulburn and Campbell Sts Liverpool, New South Wales 2170 Australia	BAF312A2304 Subjects: 10	3 to 7 Dec 2018	NAI
Site 1042 **Eva-Maria Maida, MD** Koellnerhofgasse 4/1/12 Vienna, 1010 Austria	BAF312A2304 Subjects: 42	29 Oct 2018 to 02 Nov 2018	VAI
Site 5059 **Yang Mao-Draayer, MD** 2301 Commonwealth Blvd. Ann Arbor, MI 48109	BAF312A2304 Subjects: 12	17 to 24 Oct 2018	NAI
Novartis Pharmaceutical Corporation One Health Plaza East Hanover, NJ 07936-1080	BAF312A2304	10 -14 Dec 2018	OAI*

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable
*Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Suzanne Hodgkinson, M.D

At this site for Protocol BAF312A2304, 10 subjects were screened,10 were enrolled, 4 subjects terminated early, 1 subject withdrew from the study, 5 subjects completed the Core Part of the study, and 2 of the 10 subjects enrolled in the open-label Extension Part of the study. One subject (subject (b) (6)) had their blind broken by the clinical investigator due to signs of worsening MS symptoms. Study and subject source records were reviewed during the inspection for all 10 of the enrolled subjects. Records reviewed included, but were not limited to, the study protocol and amendments, Ethics Committee reviews and approvals, subject selection criteria and informed consent, source data and case report forms, source records for the primary efficacy endpoint, financial disclosure, FDA 1572, personnel training, drug accountability, adverse event reporting, general protocol adherence, protocol deviations related to unblinding and inappropriate database access, and monitor logs and follow-up letters.

There was no evidence of under-reporting of adverse events. EDSS scores for the 10 subjects enrolled were reviewed and verified against the data listings provided by the sponsor. One discrepancy was noted in which data in the EDSS source documents did not match the sponsor's data listings for subject (b) (6) This subject was randomized to siponimod. At the Month 21 visit, the subject's EDSS ambulation score was documented as 0 on the source record at the site. However, in the sponsor's data line listings submitted to FDA showed an ambulation score of 2.

Of note there was one study coordinator who was part of the main study team who had access to the first dose database and made modifications in the first dose database. In May 2016, this study coordinator's role changed from being part of the blinded main study team during the Core Part of the study to being part of the First Dose Monitoring team during the Extension Part of the Study. She retained access to the first dose and main databases during the Extension Part of the study for the purpose of completing query resolutions from the sponsor. There were 10 subjects enrolled in the trial during the time that the study coordinator entered data and made changes to the data in the first dose database. Changes made in the first database included adding adverse event outcomes for subjects (b) (6) and (b) (6).

Reviewer's comment: It is unclear what information the study coordinator may have viewed and shared with the main study team, including the clinical investigators and EDSS raters, as a result of the access to the first dose and main databases. Therefore, we cannot rule out the introduction of bias during the study potentially affecting the reliability of the data for the 10 subjects enrolled at this site.

2. Eva-Maria Maida, M.D.

At this site for Protocol BAF312A2304, 44 subjects were screened, 42 were enrolled, 4 subjects terminated the study early, and 1 subject completed the study and chose not to enroll in the open-label Extension Part of the study. There are 38 subjects currently enrolled in the extension part of the study. Study and subject source records were reviewed during the

inspection for 12 of the 42 enrolled subjects. Records reviewed included, but were not limited to, the study protocol and amendments, Ethics Committee submissions and approvals, subject selection criteria and informed consent, source data and case report forms, source records for the primary efficacy endpoint, financial disclosure, drug accountability, adverse event reporting, protocol deviations related to unblinding and inappropriate database access, and monitor logs and follow-up letters.

There was no evidence of under-reporting of adverse events. EDSS scores for the 12 of the 42 subjects were reviewed and verified against the data listings provided by the sponsor. No discrepancies were noted. Of note at this site, one study coordinator had access to and entered and modified data in the main database while at the same time also having access to the Central NESC system, the system used to record EDSS scores. During inspection, it was noted that this study coordinator was part of the main study team. Although she had access to the Central NESC system, she was not an EDSS rater, but rather she acted as a scribe to enter EDSS scores in the NESC Central system from paper source EDSS worksheets that were completed and signed by the qualified EDSS rater. There were no other incidents observed among the blinded site study personnel (i.e., the main study team and the independent EDSS raters) where inappropriate access was granted to a database (i.e., main or first dose databases) that contained information that could potentially unblind the subject's treatment assignment.

Reviewer's comment: Although a study coordinator who was part of the main study team had access to both the main database and the NESC system, she was not an EDSS rater and did not perform EDSS assessments. The study coordinator entered the EDSS assessment scores into the NESC system from paper source records completed by the independent EDSS rater. Because the actual independent EDSS rater who completed the paper EDSS worksheets did not have access to either the first dose or main databases, the study coordinator's dual access to the main database and Central NESC system likely did not have an effect on the reliability of the EDSS scores for the 42 subjects at this site.

In addition, the protocol required the following:

> *"Documented EDSS progression in the 2 years prior to study of ≥1 point for patients with EDSS <6.0 at screening, and ≥0.5 point for patients with EDSS ≥6.0 at screening. Should documented EDSS scores not be available, a written summary of the clinical evidence of disability progression in the previous 2 years, and retrospective assessment of EDSS score from data up to 2 years prior to screening must be submitted for central review prior to enrollment."*

During inspection, it was noted that central review was received after subject enrollment for subjects (b) (6) and (b) (6) were enrolled in the study (see table below).

Subject #/Randomization	**EDSS score 2 years before screening**	**EDSS score at screening**
(b) (6) /Placebo	3.0	3.5
(b) (6) /Siponimod	3.5	4.0

Although the sponsor was informed of the protocol deviations for the two subjects; only one of the two protocol deviation, for subject (b) (6), was reported to FDA. A Form FDA-483, Inspection Observations, was issued at the end of the inspection for failure to conduct the investigation in accordance with the investigational plan for this observation. Dr. Maida accepted responsibility for the error and promised improvements in the future. No similar deviations occurred at other times in the trial for this clinical investigator.

Another deficiency noted on the Form FDA-483 that was issued at the end of the inspection was a failure to prepare and maintain adequate and accurate case histories. Specifically, the protocol inclusion criteria required that subjects have secondary progressive course of MS, defined by a progressive increase in disability (of at least 6 months duration) in the absence of relapses or independent of relapses. The criterion also notes the requirement of an "attestation by the investigator in a written statement that the disease has entered the progressive stage (according to the study definition) at least 6 months prior to enrollment." However, Dr. Maida's site did not have any such attestation on file or in the source records for the 42 subjects enrolled in the protocol. Dr. Maida and the site staff were admittedly unclear about what was needed to fulfill this inclusion requirement. Dr. Maida further stated that she believed the signed inclusion/exclusion checklist and the information in the subject's progress notes to be sufficient to meet this requirement of the protocol.

Reviewer's comments: The signed inclusion/exclusion checklists did not contain a written attestation statement by the investigator, only a checkbox to indicate that the written attestation statement was completed. In addition, other source records (e.g., progress notes for study subjects) were reviewed and no written attestations by the investigators were noted. Although the finding is a regulatory violation, not having an "attestation by the investigator in a written statement that the disease has entered the progressive stage," is unlikely to significantly affect the overall reliability of the safety and efficacy data as subjects at this site were enrolled after meeting the other protocol specified inclusion criteria.

3. Yang Mao-Draayer, M.D.

At this site for Protocol BAF312A2304, 16 subjects were screened, 12 were enrolled. As reported in the Clinical Study Report, 3 subjects terminated the study early and there were 9 subjects who entered and completed the open-label Extension Part of the study. Study and subject source records were reviewed during the inspection for all 12 enrolled subjects. Records reviewed included, but were not limited to, the study protocol and amendments, Institutional Review Board reviews and approvals, subject selection criteria and informed consent, source data and case report forms, source records for the primary efficacy endpoint, financial disclosure, FDA 1572, personnel training, drug accountability, adverse event reporting, general protocol adherence, protocol deviations related to unblinding and inappropriate database access, and monitor logs and follow-up letters.

There was no evidence of under-reporting of adverse events. EDSS scores for the 12 subjects enrolled were reviewed and verified against the data listings provided by the sponsor. No

discrepancies were noted. Of note at this site, one study coordinator had access to both the first dose and main databases for a 7 month period in 2014 (from 02 Mar 2014 to 01 Oct 2014). During the time period of dual database access, 5 subjects were enrolled and treated in the study. During inspection, it was noted that this study coordinator, who is no longer employed at the site, was a First Dose Administrator who also had inappropriate access to the main database, rather than part of the main study team.

Reviewer's comment: Because First Dose Administrators are considered unblinded study personnel, this study coordinator's dual database access likely did not have an effect on the reliability of the study data for the subjects enrolled during the time period of dual database access. Of note, in the Clinical Study Report, Amendment 1, dated 19 July 2018, Novartis initially classified the protocol deviations for dual database access for this site as GCP01, a main database user who had inappropriate access to the first dose database. During the sponsor inspection, we clarified that this study coordinator's role in the study was as a First Dose Administrator, hence a first dose database user who had inappropriate access to the main database (i.e., protocol deviation should have been classified as GCP10, and not GCP01).

4. Novartis Pharmaceuticals Corporation

The inspection of Novartis Pharmaceuticals Corporation focused on the control, oversight, and management of Protocol BAF312A2304. In addition, the inspection focused on obtaining further information on protocol deviations related to inappropriate access to the first dose and main databases used in the study by study personnel at the sites, Novartis Clinical Research Associates (CRAs), and other Novartis personnel. This information was used to assess the impact that the inappropriate database access had on the integrity of the study blind and ultimately the reliability of the study data.

Novartis was responsible for monitoring the study and Novartis CRAs conducted both onsite and remote monitoring activities. It was noted during the inspection that Novartis' CRAs were responsible for granting and revoking access by completing and approving a form that was subsequently sent to a vendor (b) (4) contracted by Novartis, who among other IT services, created and inactivated user accounts for the first dose and main databases. A Form FDA-483 was issued at the end of the inspection, which included an observation of failure to ensure proper monitoring of the investigation. Novartis did not have sufficient procedures outlined in their monitoring plan for granting and revoking access as well as detecting inappropriate access to databases that contained study information that could be potentially unblinding. Novartis CRAs did not properly grant study personnel (e.g., study coordinators, investigators, and EDSS raters) access to the databases used in the trial. In addition, the CRAs failed to identify cases where inappropriate database access was granted to site personnel.

During the inspection, we observed the following:

- 62 (21%) clinical sites (out of 294 total clinical sites) in which site personnel were granted and had inappropriate access to the first dose or main databases affecting 285 (17%) out of 1651 total study subjects. This access involved:
    - 32 users of the main database who had inappropriate access to the first dose database potentially affecting 101 subjects; 5 of the 32 made data modifications in the first dose database on 11 subjects
    - 41 users of the first dose database who had inappropriate access to the main database potentially affecting 142 subject; 5 out of the 41 made data modifications in the main database
    - 3 EDSS raters who had inappropriate access to the first dose database potentially affecting 7 subjects
    - 9 EDSS raters who had inappropriate access to the main database potentially affecting 57 subjects; 2 of 9 users made data modifications in the main database

      Of note, there were 22 total subjects for which there was overlap across the 4 categories identified above (including one EDSS rater who conducted EDSS assessments for 2 subjects). Thus, the total number of subjects affected is 285 and the total number of subjects affected by the EDSS raters with dual database access was 62.

- Furthermore, there were also 77 Clinical Research Associates (CRAs) who had inappropriate database access:
    - 40 CRAs who were assigned to the first dose database had inappropriate access to the main database
    - 37 CRAs who were assigned to the main database had inappropriate access to the first dose database

Novartis stated in writing to FDA in a response to an Information Request, dated 23 August 2018, and also during inspection that Novartis did not retain system access audit trails to either the first dose or main databases. Because there were no system access audit trails available to review, it is difficult to know if users who had inappropriate access to these databases viewed and used the data during the course of the trial and if biases were introduced when performing the study assessments.

Finally, the protocol inclusion criteria required that subjects must have secondary progressive course of MS, defined by a progressive increase in disability (of at least 6 months duration) in the absence of relapses or independent of relapses. The criterion also notes the requirement of an "attestation by the investigator in a written statement that the disease has entered the progressive stage (according to the study definition) at least 6 months prior to enrollment. While the written attestation from the investigator was required by the protocol in order for subjects to be included in the protocol, Novartis had no clear guidance and formal procedure for documenting the written attestations at the sites. During inspection, Novartis was unable to provide signed attestations for all subjects enrolled in the protocol, Novartis provided instead an example of an inclusion/exclusion worksheet that sites had the option to use to document (via a checkmark in a box) that the written attestation statement was completed. In

addition, Novartis stated that the written attestation was documented in the source documents located at the sites. However, during inspection of Site 1042, written attestations in the source documents were not available for the subjects enrolled at this site.

Reviewer's comment: The protocol inclusion criteria requirement of an "attestation by the investigator in a written statement that the disease has entered the progressive stage (at least 6 months prior to enrollment) was not sufficiently documented at the sites. Although the sponsor should have ensured the sites followed the protocol inclusion criteria requirement, not having an these attestations is unlikely to significantly affect the overall reliability of safety and efficacy data as subjects at the sites inspected were enrolled after meeting the other protocol specified inclusion criteria.

{See appended electronic signature page}

Cheryl Grandinetti, Pharm.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Kassa Ayalew, M.D., M.P.H Branch Chief
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DNP /Medical Officer/David Jones
DNP/ Clinical Team Leader/ Paul Lee
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OSI/ GCP Program Analysts/Yolanda Patague
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/s/

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KASSA AYALEW
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DIVISION OF PULMONARY, ALLERGY, AND RHEUMATOLOGY PRODUCTS
MEDICAL OFFICER CONSULTATION

Date:	January 17, 2019
To:	Division of Neurology Products (DNP)
From:	Rekha Jhamnani, Medical Officer, DPARP
Through:	Miya Paterniti, Medical Team Leader, DPARP
Through:	Banu Karimi-Shah, Acting Deputy Director, DPARP
Subject:	Siponimod

General Information

NDA/IND#:	209884
Sponsor:	Novartis
Drug Product:	Siponimod (Mayzent)
Request From:	Division of Neurology Products
Date of Request:	October 26, 2018
Date Received:	October 26, 2018
Requested completion date:	January 17, 2018
Materials Reviewed:	Gilenya DPARP Consult (April 8, 2010) Original NDA Submission (March 28, 2018): Clinical Overview Multiple Sclerosis, Summary of Clinical Safety, Synopses of Individual Studies, BAF312A2304 Clinical Study Reports. Response to Information Request (December 14, 2018), Pulmonary Function Testing analysis. Response to Information Request (January 11, 2019), Pulmonary Function Testing analysis.

I. Introduction

This is a Medical Officer response to the consultation request from the Division of Neurological Products (DNP), to review pulmonary function results for NDA 209884 for siponimod, a new oral sphingosine-1-phosphate (S1P) receptor modulator proposed for the treatment of multiple sclerosis. DNP has also requested for the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) to specifically comment on whether siponimod is associated with dose-dependent reductions in FEV1 and DLCO that should be reflected in the label.

The sponsor conducted a single pivotal efficacy and safety study (A2304) that informed siponimod's label and is the primary source of pulmonary function data. An overview of study A2304 is provided below. The sponsor also conducted a double-blind, randomized, placebo-controlled, parallel-group, adaptive, dose-ranging study (A2201) in patients with relapsing-remitting multiple sclerosis. Pulmonary function data is also included from this study to assess dose effect.

II. Background

Siponimod (BAF312A) is a new oral sphingosine-1-phosphate (S1P) receptor modulator, which is selective for S1P1 and S1P5. Sphingolipids are components of the cell membrane that provide structural integrity. S1P receptor modulation leads to retention of autoreactive lymphocytes in lymph nodes to reduce infiltration of these lymphocytes into the central nervous system.[1] Though the target indication for siponimod is secondary progressive multiple sclerosis (MS), the drug is also being evaluated in relapsing-remitting multiple sclerosis. Siponimod was studied in two well-controlled randomized, double-blind, multi-center, placebo-controlled clinical trials: A2201 was a dose-ranging study in relapsing-remitting multiple sclerosis and A2304 was the pivotal efficacy and safety study in secondary progressive multiple sclerosis.

Prior to siponimod, fingolimod (NDA 22527), another oral S1P receptor modulator, was approved in September 2010 for relapsing-remitting multiple sclerosis. DPARP was consulted (see consult April 8, 2010) for fingolimod-related changes in pulmonary function. S1P regulates the functions of airway smooth muscles during inflammation and airway remodeling. Thus, the involvement of S1P signaling has been confirmed in various diseases including lung disease.[2,3] Based on safety findings, DPARP recommended that DNP include information in their label regarding drug-associated decline in pulmonary lung function. The current fingolimod label (revised 10/2018) states under Section 5.6:

"Dose-dependent reductions in forced expiratory volume over 1 second (FEV1) and diffusion lung capacity for carbon monoxide (DLCO) were observed in patients treated with GILENYA as early as 1 month after treatment initiation. In 2-year placebo-controlled trials in adult patients, the reduction in baseline in the percent of predicted values for FEV1 at the time of last assessment on drug was 2.8% for GILENYA 0.5mg and 1.0% for placebo. For DLCO, the reduction from baseline in percent of predicted values at the time of last assessment on drug was 3.3% for GILENYA 0.5mg and 0.5% for placebo. The changes in FEV1 appear to be reversible after treatment discontinuation. There is insufficient information to determine the reversibility of the decrease of DLCO after drug discontinuation. In MS placebo-controlled trials in adult patients, dyspnea was reported in 9% of patients receiving GILENYA 0.5mg and 7% of patients receiving placebo. Several patients discontinued GILENYA because of unexplained dyspnea during the extension (uncontrolled) studies. GILENYA has not been tested in MS patients with compromised respiratory function. Spirometric evaluation of respiratory function and evaluation of DLCO should be performed during therapy with GILENYA if clinically indicated."

Although not included in labeling, the absolute FEV1 decline ranged from 104 mL to 220 mL depending on the dose and study. The reversibility statement was based on 3-month post-study pulmonary function tests (PFTs) in a subset of patients (about 180 subjects), suggesting that the downwards trends from baseline in PFT parameters had begun to reverse. DPARP recommended further study of pulmonary safety to evaluate the stability and reversibility of declines in pulmonary function associated with chronic fingolimod treatment. DNP included a post-marketing requirement (PMR) for an observational prospective, parallel cohort (patients newly prescribed fingolimod vs. patients receiving other disease modifying therapy) study in relapsing multiple sclerosis patients which

included assessment of pulmonary toxicity, among other safety outcomes. The sponsor reports difficulties with recruitment for this study.

II. Study Summary

A. Study Overview: A2304

Study Design: Phase 3 multicenter, randomized, double-blind, parallel-group, placebo-controlled, variable treatment duration study evaluating the efficacy and safety of siponimod in patients with secondary progressive multiple sclerosis followed by extended treatment with open-label siponimod. Patients were randomized 2:1 study drug to placebo and underwent treatment for 3 years after randomization. The drug was up-titrated from 0.25 to 0.5 to 0.75 to 1.25 to 2 mg daily (target dose) and patients with low lymphocyte counts were up-titrated to only 1mg daily. Currently there is an ongoing extension portion to A2304 that began in 2015 that will last up to 7 years, in which patients will receive open-label siponimod.

Primary Endpoint:

- Time to 3-month Confirmed Disability Progression in patients with secondary progressive MS via Expanded Disability Status Scale (EDSS)

B. Patient Population

Number of Subjects: Randomization of 1635 ambulatory adults with a diagnosis of MS with a secondary progressive disease course

Key Inclusion Criteria:

- Males or females aged 18 to 60 years (inclusive) with prior history of relapsing-remitting MS according to 2010 Revised McDonald criteria or secondary progressive MS defined by progressive increase in disability of at least 6 months duration in the absence of relapses
- EDSS 3.0-6.5 inclusive
- EDSS progression in 2 years prior to study
- No relapse or corticosteroid treatment 3 months prior to randomization

Key Exclusion Criteria

- History of active severe respiratory disease, including chronic obstructive pulmonary disease or pulmonary fibrosis
- Tuberculosis, unless successfully treated
- Severe asthma or asthma requiring regular treatment with oral steroids
- Chronic disease of immune system other than MS
- Pregnant or nursing women, women of child-bearing potential unless using contraception during dosing and for 30 days after the last dose
- Malignancy within past 5 years
- Diabetes mellitus unless well controlled without organ complications
- Macular edema during randomization phase

- Systemic infection including HIV/AIDS, Hepatitis A,B,C, E
- Live vaccine within 2 months prior to randomization
- History of siponimod use, fingolimod within 2 months prior to randomization or use for more than 6 months, intravenous immunoglobulin or dimethyl fumarate within 2 months prior to randomization, natalizumab or chemotherapeutics within 6 months prior to randomization
- Hypersensitivity

Reviewer Comments: Although subjects with active severe respiratory disease were excluded, subjects with mild to moderate asthma and COPD could be enrolled. These subjects were included in an expanded pulmonary monitoring group.

Subjects with mild to moderate asthma or COPD, who were included in an expanded pulmonary monitoring group, underwent more frequent pulmonary monitoring, as outlined in **Table 1**. The overall population also underwent PFT monitoring at screening, months 3, 12, 24, 36, end of treatment, and end of study.

Table 1. Pulmonary assessments for the Expanded Pulmonary Monitoring Group

Visit	SCR	BL	D28	M3	M6	M12	M15	M18	M24	M30/M42/M54	M36/M48	EOT/EOS
PFT	X		X	X	X	X	X	X	X	X	X	X
HRCT		X							X			X

Source: Table 9-5 baf312a2304 legacy clinical study report p. 111

The Extension Part of study A2304 included pulmonary function testing in the expanded pulmonary group at baseline, months 1, 3, 6, 12 and every 6 months thereafter. The overall group underwent pulmonary function testing at baseline, months 3 and 6, and every 12 months thereafter.

C. Safety

Safety monitoring includes adverse events, serious adverse events, laboratory testing, serum pregnancy testing, vital signs, ECG, body weight, physical exam, pulmonary function tests, ophthalmologic examinations, chest x-ray or High-Resolution Computer Tomography (HRCT), and dermatologic abnormality assessment.

Summary statistics for PFT parameters included change from baseline in absolute and percent predicted FEV1, FVC, FEV1/FVC, and corrected DLCO. It is not clear if the sponsor used ATS/ERS criteria for assessment of PFTs.

III. Pulmonary Results

An information request was sent to the sponsor requesting the treatment difference between siponimod and placebo for FEV1 and DLCO with a statistical comparison including 95% confidence interval for studies A2201 and A2304 in both the safety population and expanded pulmonary monitoring group. We also asked for baseline demographics and characteristics table for the expanded pulmonary monitoring group including age, sex, race, underlying pulmonary diagnosis, smoking history, concomitant

medications, mean FEV1 at baseline, percent predicted FEV1 at baseline, percent FEV1 reversibility, mean percent predicted DLCO at baseline, and GOLD stage for patients with COPD. The sponsor did not provide the GOLD stage for patients with COPD.

Another information request was sent to the sponsor January 4, 2019 asking for FEV1 data for patients at time points after study drug discontinuation and how often spirometry is monitored in the extension study. Furthermore, we asked the sponsor for change from baseline treatment difference between treatment and placebo for percent predicted FEV1 and DLCO at all available timepoints. Our review focused on the response to these IRs dated December 14, 2018 and January 11, 2019.

Patient demographics

The patient demographics for the overall patient population and the expanded pulmonary monitoring group are displayed in (Table 2).

Table 2. Baseline Demographics in overall study population and the expanded pulmonary monitoring group

N (%)	Siponimod Overall n=1105	Placebo Overall n=546	Siponimod Expanded n=38	Placebo Expanded n=21
Age mean (years)	48	48.1	48.1	48.8
Female	669 (60.5)	323 (59.2)	26 (68.4)	10 (47.6)
White	1050 (95)	513 (94)	37 (97.4)	16 (76.2)
Asian	31 (2.8)	18 (3.3)	0 (0)	1 (4.8)
Other	12 (1.1)	7 (1.3)	1 (2.6)	1 (4.8)
Black	7 (0.6)	3 (0.5)	0 (0)	1 (4.8)
Unknown	5 (0.5)	5 (0.9)	0 (0)	2 (9.5)
History of Asthma	40 (3.6)	23 (4.2)	23 (60.5)	15 (71.4)
History of COPD			3 (7.9)	2 (9.5)
Current Smoker			12 (31.6)	3 (14.3)
Former Smoker			9 (23.7)	9 (42.9)
Never Smoker			17 (44.7)	9 (42.9)
Baseline FEV1 mean (L)			2.7	2.9
Baseline FEV1 mean (% predicted)			87.6	91.7
Inhaled Short-acting beta agonist use			14 (36.8)	7 (33.3)
Inhaled corticosteroid use			8 (21.1)	1 (4.8)
Inhaled anticholinergic use			1 (2.6)	0 (0)
Inhaled corticosteroid/long-			5 (13.2)	5 (23.8)

acting beta agonist use				
Oral leukotriene inhibitor use			3 (7.9)	2 (9.5)
Source: Table 11.2.1 baf312a2304 legacy clinical study report p. 167 and Table 7.2.1 Information Request baf312a-pft-analysis p. 12-33				

The average subject in the overall population was 48 years of age, female, and white. The expanded pulmonary monitoring group demographics were similar. We asked for the sponsor to provide additional baseline history and medication use for the expanded pulmonary set. Although the overall population had 63 subjects with a history of asthma, only 38 were included in the expanded pulmonary monitoring group because a few patients only had asthma included in their Medical History Case Report Form and not their Pulmonary Function Test Case Report Form. Twenty patients had a history of asthma in the distant past or had mild asthma not requiring treatment at the time of study entry. The majority subjects in the expanded pulmonary monitoring group had asthma. About half of the subjects had a smoking history. The average baseline FEV1 was 2.7-2.9 L with a percent predicted FEV1 of 88-92%. The baseline medication use is what would be expected for a mild-moderate asthma or COPD population, although it is unclear if any of these subjects were taking more than one medication group.

Pulmonary function tests

The absolute change in FEV1 results were reviewed for Study A2304 for the overall population (Table 3) and the expanded pulmonary monitoring group (Table 4).

Table 3. Change from baseline in FEV1 (L) by visit window in overall population - Study A2304

Visit Window	Siponimod n= 1032	Placebo n= 522	Difference	Confidence Interval
Month 3	-0.070 n=998	-0.001 n=504	-0.069	(-0.098, -0.040)
1 year	-0.113 n=885	-0.050 n=432	-0.063	(-0.098, -0.029)
2 years	-0.150 n=454	-0.062 n=206	-0.088	(-0.139, -0.037)
3 years	-0.212 n=37	0.106 n=10	-0.318	(-0.054, -0.132)
Source: Table 7.1.1 Information Request baf312a-pft-analysis p. 1				

For the overall population the absolute change in FEV1 compared to placebo was statistically significant starting at the first time point (month 3). This difference increased over time from 69 mL at month 3 to 88 mL at 2 years. The 3 year timepoint is not reliable given the small number of subjects included at this timepoint. This is evident by the large increase in FEV1 in the placebo group which is driving the large FEV1 treatment

difference. The changes in absolute FEV1 compared to placebo up to 2 years were similar to changes in absolute FEV1 seen with fingolimod.

The changes in percent predicted FEV1 in the overall population (siponimod compared to placebo) were -2.4% at month 3, -2.1% at 1 year, and -2.8% at 2 years. The 3-year timepoint once again is not reliable due to the small number of subjects included at this timepoint. In the expanded pulmonary monitoring group, the changes in percent predicted FEV1 were -4.0% at month 3 and -6.1% at 1 year. Data for the 3-year timepoint was not provided.

Table 4. Change from baseline in FEV1 absolute value in liters by visit window in expanded pulmonary monitoring group - Study A2304

Visit Window	Siponimod n=36	Placebo n= 18	Difference	Confidence Interval
Month 3	-0.116 n=35	0.001 N=17	-0.117	(-0.282, 0.048)
1 year	-0.150 n=33	0.046 n=15	-0.196	(-0.351, -0.040)
2 years	-0.300 n=13	0.032 n=3	-0.332	(-0.816, 0.152)
Source: Table 7.1.4 Information Request baf312a-pft-analysis p. 4				

For the expanded pulmonary monitoring group (subjects with mild to moderate asthma or COPD), the decrease in FEV1 compared to placebo was statistically significant at 1 year, but not at month 3 or 2 years. The trends are important here, but as the sample size was small, it is not expected that these treatment differences would be statistically significant. Three-year data was not provided.

We also reviewed the FEV1 results for A2201 to assess if there was a dose-dependent change (**Table 5**).

Table 5. Change from baseline in FEV1 (L) Treatment Difference by visit window and dose - Study A2201

	Siponimod 0.25mg	Siponimod 0.5mg	Siponimod 1.25mg	Siponimod 2mg	Siponimod 10mg
Month 1 (95% CI)	n=49 -0.045 (-0.195, 0.106)	n=44 0.014 (-0.080, 0.107)	n=39 -0.129 (-0.259, 0.001)	n=44 -0.029 (-0.114, 0.057)	n=44 -0.141 (-0.255, -0.027)
Month 3 (95% CI)	n=48 -0.009 (-0.149, 0.130)	-	n=36 -0.080 (-0.223, 0.063)	-	-
Month 6 (95% CI)	-	n=33 0.011 (-0.103, 0.125)	-	n=33 -0.099 (-0.198, 0.001)	n=33 -0.146 (-0.284, -0.007)
Source: Table 7.1.11 and Table 7.1.10 Information Request baf312a-pft-analysis p.7-11					

There was a dose-dependent treatment difference for FEV1 noted at months 3 and 6. As this was a small study, the decrease in FEV1 was not statistically significant; however, the trend is notable. The trend in dose-dependent decreases in lung function led credence to the lung function effect seen in the pivotal trial A2304.

In general, the decline in FEV1 worsened over time and was dose-dependent, reflecting a general trend towards cumulative decline in pulmonary function due to siponimod.

The sponsor provided FEV1 assessment performed 14 days after the last dose of study drug in 111 subjects treated with siponimod and 46 subjects treated with placebo in the response to the January 3, 2019 information request. The changes in FEV1 were similar to the last on treatment assessment without evidence of reversibility. It is unlikely that 14 days is an adequate time period off drug to assess reversibility. The numbers of subjects with off-treatment FEV1 assessments was also small.

The sponsor was unable to provide PFT data from the ongoing 7-year extension study. The 7-year extension study does not include a control group. Although it may be helpful to review this data once it is available, the control group is an essential component of interpreting FEV1 data over time as there is physiologic declines in FEV1 over time that are not specifically defined. There are currently no post-marketing requirements proposed by the Applicant with respect to pulmonary-associated adverse effects. DPARP recommends further study of pulmonary safety to evaluate the stability and reversibility of declines in pulmonary function associated with chronic siponimod treatment.

There were no notable changes in DLCO.

Pulmonary AEs

Respiratory adverse events were reviewed and are summarized in Table 6.

Table 6. AES for the Respiratory, Thoracic, and Mediastinal SOC (Drug greater than placebo and ≥2 events)

Preferred Term	Siponimod n (%)	Placebo n (%)
Asthma	4 (0.4)	1 (0.2)
Nasal congestion	4 (0.4)	1 (0.2)
COPD	3 (0.3)	1 (0.2)
Dysphonia	3 (0.3)	1 (0.2)
Nasal dryness	3 (0.3)	1 (0.2)
Respiratory disorder	3 (0.3)	0
Choking sensation	2 (0.2)	0
Source: Study A2304 CSR, Table 14.3.1-1.1 p. 13151		

The most common respiratory AE was Asthma. There were no reported serious respiratory AEs or AEs leading to death.

Five patients in the siponimod group (versus zero in the placebo group) had changes in pulmonary function testing that lead to study drug discontinuation as noted in (Table 7).

Table 7. Respiratory AEs leading to permanent study drug discontinuation		
	Siponimod n (%)	Placebo n (%)
Pulmonary function test decreased	3 (0.3)	0
Carbon monoxide diffusing capacity decreased	2 (0.2)	0
Source: Study A2304 CSR, Table 12-13 p. 229		

Study drug interruption was required in patients who had reductions in FEV1, FVC, or corrected DLCO below 60% of pre-treatment value at any visit and those patients were to be referred to a pulmonary specialist. A brief narrative for the 5 subjects discontinued for respiratory AEs is listed below:

Pulmonary function test decreased

1. A 49-year old female with secondary progressive MS had evidence of worsening of MS and decreased pulmonary function testing on Day 373 of study drug.
2. A 46-year old female who was an active smoker with secondary progressive MS had changes in DLCO and FVC on Day 96 of study drug, and study drug was discontinued. On Day 117, PFTs remained depressed.
3. A 48-year old male had elevations in liver enzymes and decreased DLCO on Day 374 of study drug, wherein the drug was discontinued. Approximately 2 weeks after discontinuation, pulmonary function testing returned to normal.

Carbon monoxide diffusing capacity decreased

1. A 46-year old female who had a 12-pack year smoking history. She was hospitalized due to urge incontinence and after discharge from the hospital was found to have a decreased DLCO of 34% predicted (baseline was 57% predicted). This lead to hospitalization and pulmonologist evaluation and she was diagnosed with middle grade reduction in lung volume and restrictive lung disease.
2. A 52-year old female with secondary progressive multiple sclerosis who had evidence of decreased diffusing capacity for carbon monoxide on Day 71 of study drug.

In the extension part of study A2304, there were 17 additional SAEs related to respiratory, thoracic, and mediastinal disorders as of the 120-day safety cutoff of December 31, 2018. Of these, 8 discontinued siponimod treatment. The SAEs by preferred term included aspiration pneumonia, respiratory arrest, pulmonary embolism in three patients, laryngeal stenosis, respiratory paralysis, hyperventilation, pneumothorax in two patients, COPD exacerbation, asthma and parainfluenza virus, decreased pulmonary function test in two patients, decreased carbon monoxide diffusing capacity, respiratory failure with pneumonia, and dyspnea in two patients.

IV. Labeling Recommendations

Based on our review of pulmonary function test results, we recommend that siponimod, like fingolimod, include verbiage in Section 5 of the label to reflect observed changes in FEV1 as outlined below.

Dose-dependent reductions in absolute forced expiratory volume over 1 second (FEV1) were observed in patients treated with MAYZENT as early as 3 months after treatment initiation. In a placebo-controlled trial in adult patients, the decline in absolute FEV1 from baseline compared to placebo was 88 mL (95% CI: 139, 37) at 2 years. The mean difference between siponimod and placebo in percent predicted FEV1 at 2 years was 2.8% (95% CI: -4.5, -1.0) . There is insufficient information to determine the reversibility of the decrease in FEV1 after drug discontinuation. In MS controlled trials, several patients discontinued MAYZENT because of decreases in pulmonary function testing. MAYZENT has been tested in MS patients with mild to moderate asthma and chronic obstructive pulmonary disease. The changes in FEV1 were similar in this subgroup compared with the overall population. Spirometric evaluation of respiratory function should be performed during therapy with MAYZENT if clinically indicated.

Other Recommendations

Considering the respiratory safety profile which is notable for SAEs including respiratory arrest, pulmonary embolism, respiratory paralysis, hyperventilation, pneumothorax, COPD, asthma, decreased pulmonary function test, decreased carbon monoxide diffusing capacity, and dyspnea in additional to discontinuations due to respiratory AEs, DNP should consider the respiratory safety profile in the context of the risk-benefit assessment for siponimod.

The decline in FEV1 is similar to fingolimod; however, reversibility has not been clearly established. Although it may be helpful to review the pulmonary function data from the 7-year extension study once it is available, as it is not controlled, the pulmonary function data is unlikely to definitely establish FEV1 reversibility and stability. There are currently no post-marketing requirements proposed by the Applicant with respect to pulmonary-associated adverse effects. DPARP recommends further study of pulmonary safety to evaluate the stability and reversibility of declines in pulmonary function associated with chronic siponimod treatment.

V. References

1. Groves A, Kihara Y, Chun J. Fingolimod: direct CNS effects of sphingosine 1-phosphate (S1P) receptor modulation and implications in multiple sclerosis therapy. J Neurol Sci (2013) 328(1-2): 9-18.

2. Ammit AJ, Hastie AT, Edsall LC, Hoffman RK, Amrani Y, Krymskaya VP, et al. Sphingosine 1-phosphate modulates human airway smooth muscle cell functions that promote inflammation and airway remodeling in asthma. FASEB J (2001) 15(7):1212–4.10.1096/fj.00-0742fje

3. Mohammed S, Harikumar KB. Sphingosine 1-Phosphate: A Novel Target for Lung Disorders. Front Immunol (2017) 8: 296.

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/s/

REKHA D JHAMNANI
01/17/2019 02:39:46 PM

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01/17/2019 08:54:26 PM

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: December 14, 2018

From: CDER DCRP QT Interdisciplinary Review Team

Through: Christine Garnett, Pharm.D.
Clinical Analyst
Division of Cardiovascular and Renal Products /CDER

To: Nahleen Lopez, RPM
DNP

Subject: QT-IRT Consult to NDA 209884 (SDN 0001)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 12/6/2018 requesting a review of the observed PR prolongation in a DDI study. The QT-IRT reviewed the following materials:

- Previous QT-IRT review(s) for NDA 209884 dated 10/12/2018 in DARRTS;
- Data sets for study A2116 submitted;
- A2116 study report (NDA 209884 SDN 0001; link); and
- Clinical Safety review for fingolimod (NDA 22-527; DARRTS 08/25/2010).

1 QT-IRT Responses

Question: Clin Pharm would like a review of the PR interval prolongation observed in a DDI study (A2116). We would like to have input on whether the PR interval prolongation observed in the combination treatment (siponimod+ propranolol) arm in DDI study(A2116) raise any concern from QT perspective.

QT-IRT's response: The observed change in the PR interval in one of the combination groups (group B) at one time-point, at one day is likely a by chance finding. We are concluding this because the thorough QT study did not show any changes in the PR interval at steady-state for 2 and 10 mg siponimod when administered by itself and there was lack of internal consistency for PR prolongation in DDI study when administered together with propranolol. In the DDI the apparent PR prolongation finding was only observed on day 20 at 6.5 h not 2.5 h; only observed in group B (propranolol + siponimod), not group A (siponimod + propranolol). Furthermore, the

study did not include replicate ECGs and the variability in PR measurement in this study were high (SD = 11 ms) compared to the TQT study (8 ms).

Additionally, we were unable to locate information about how the PR intervals were measured in this study and we were unable to reproduce the graphical summaries from the sponsor. Related to the last point, the sponsor provided a table with the results, which appear inconsistent with the graphical summary.

2 BACKGROUND

2.1 Product Information

Siponimod is a sphingosine-1-phosphate (S1P) receptor modulator that is being proposed for the treatment of patients with secondary progressive multiple sclerosis (PMS). Of note, transient changes in HR and PR have been observed for other S1P receptor modulators.

We have previously reviewed the results of a thorough QT study for siponimod (DARRTS 10/12/2018). The thorough QT study was a parallel group study with three arms: siponimod, placebo and a positive-control (moxifloxacin). In this study siponimod was titrated from 0.25 mg to 10 mg over 18 days and ECGs were collected on day 10 (2 mg) and day 18 (10 mg).

Prolongation of the QTc interval was observed in the thorough QT study and the increase was comparable between 2 mg (day 10) and 10 mg (day 18) doses. The mechanism of the observed QTc prolongation does not appear to be hERG mediated.

A decrease in HR (-7 bpm) was observed for the 2 mg dose (day 10), but no changes were observed for the 10 mg dose (day 18). No changes in PR were observed for 2 mg (day 10), but a slight decrease was observed for 10 mg (day 18). While, this study does not allow for characterizing transient effects of siponimod, it does support an absence of PR and HR changes at steady-state for 2 and 10 mg.

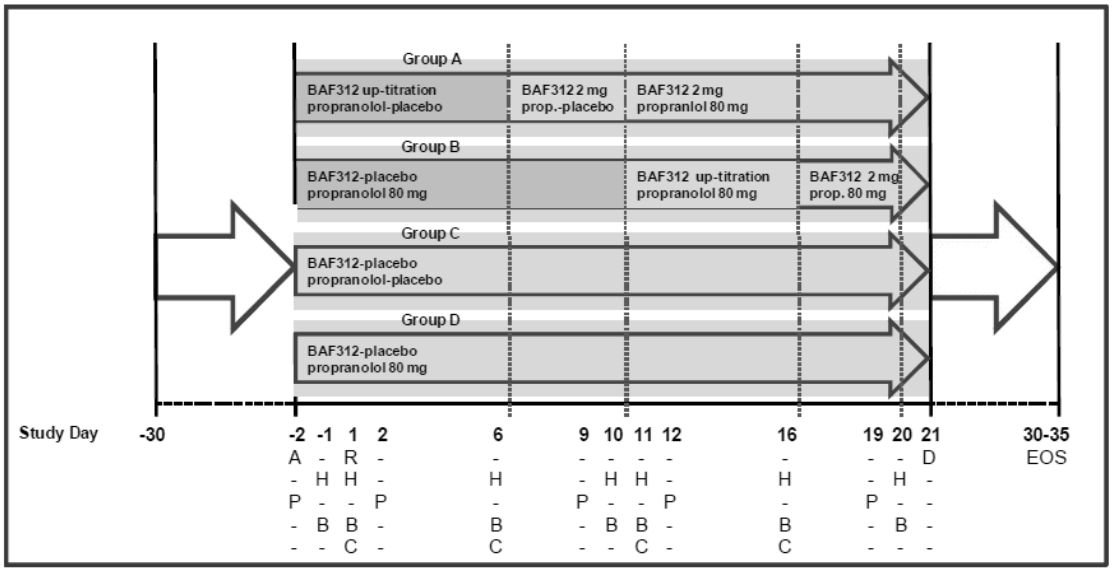
2.2 Study A2116

Study A2116 is a double-blind, randomized, placebo-controlled, parallel-group study in healthy volunteers. The study includes four parallel dose groups: A: siponimod + propranolol; B: propranolol + siponimod; C: propranolol; D: placebo (Figure 1). The study enrolled 19 subjects in each of the four groups.

Holter ECGs were collected on baseline and days 1, 6, 10, 11, 16 and 20. From the holter ECGs the primary endpoint (maximum mean change in HR) was derived. Additionally, PR measurements were based on ECGs extracted during two extraction windows (2.5 and 6.5 h post-dose). During the ECG extraction window, the subjects must be in supine rest for 5 min prior to extraction and for 10 min following the start of the extraction. Information about whether the PR intervals were overread is not available and based on the provided data sets it appears that the sponsor did not collect ECGs in replicates. Of note, the provided datasets for this study did not include mean HR measurements for the 2.5 and 6.5 h time-points. To resolve this, the reviewer mapped the HR data to PR based on the collection time. For 11 of the PR measurements, it was not possible to map a HR measurement.

The rationale for the selection of the 2.5 and 6.5 h post-dose time-points were not provided in the report and the observed T_{max} for siponimod and propranolol was 4 and 6 h respectively in this study (Figure 2).

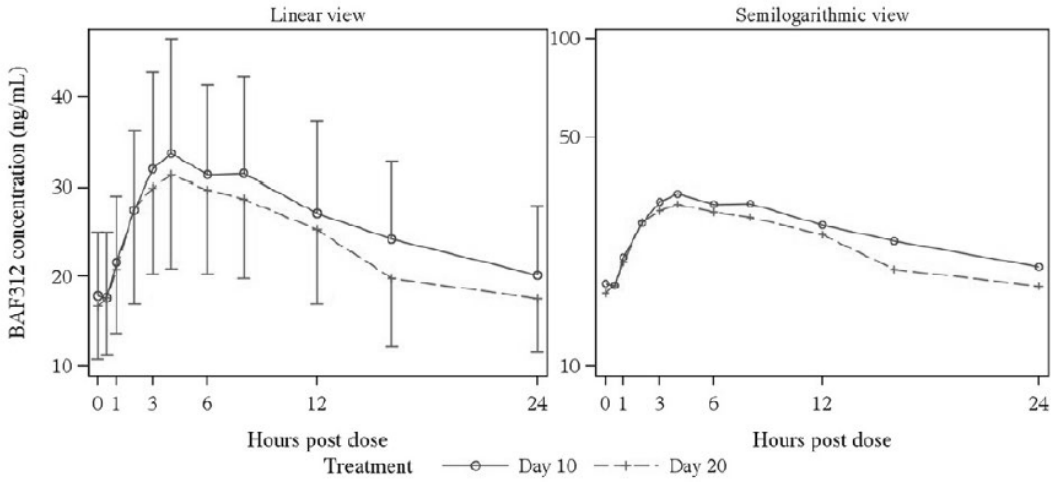
Figure 1: Study design for study A2116

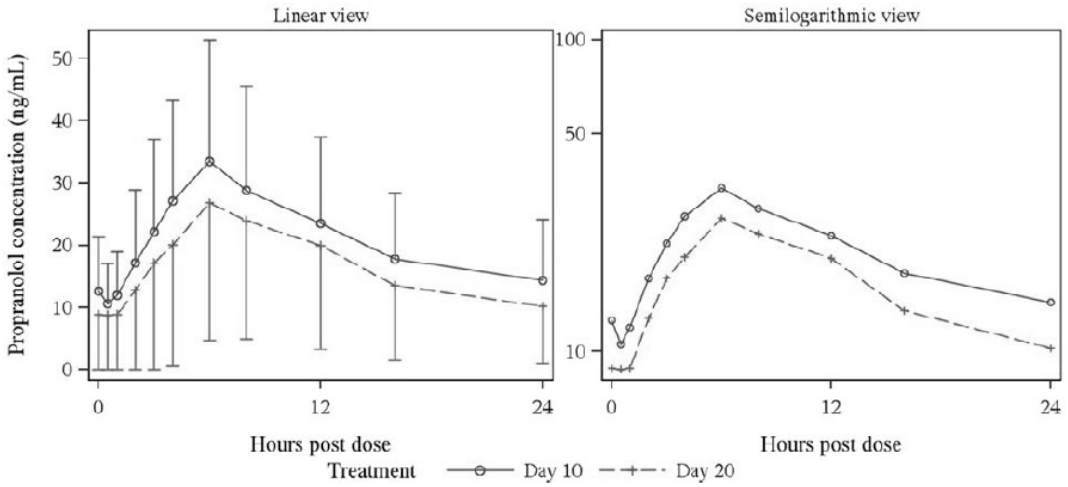


A: admission to clinic for domiciled stay
B: blood pressure profile
C: cardiac monitoring (telemetry)
D: discharge from clinic
H: Holter assessment
P: pulmonary function test (spirometry)
R: randomization
EOS: end of study visit

Source: A2116 study report, Figure 9-1

Figure 2: Arithmetic mean (SD) PK time-profile for siponimod (top row) and propranolol (bottom row)

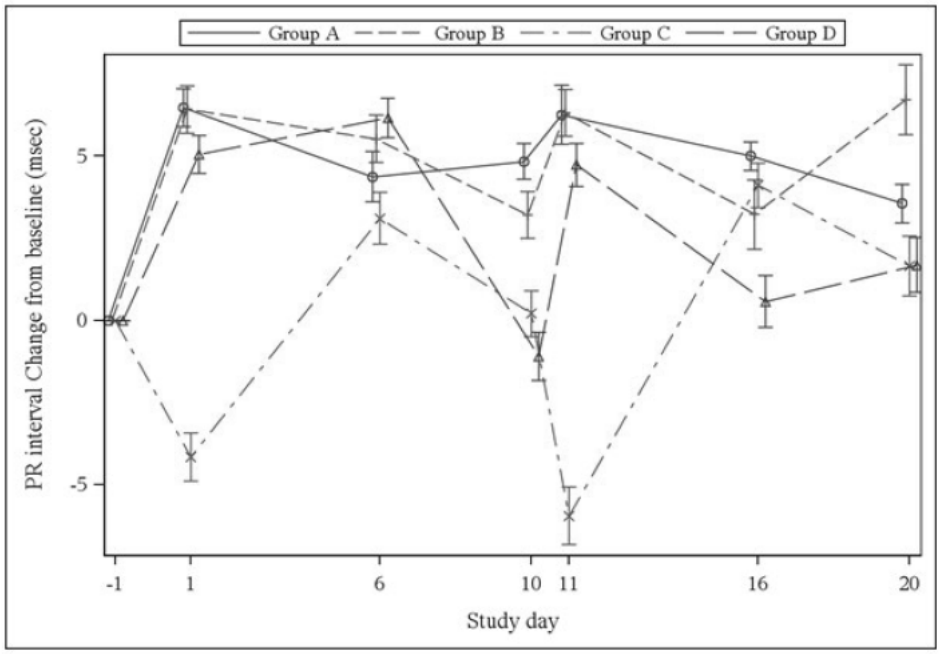


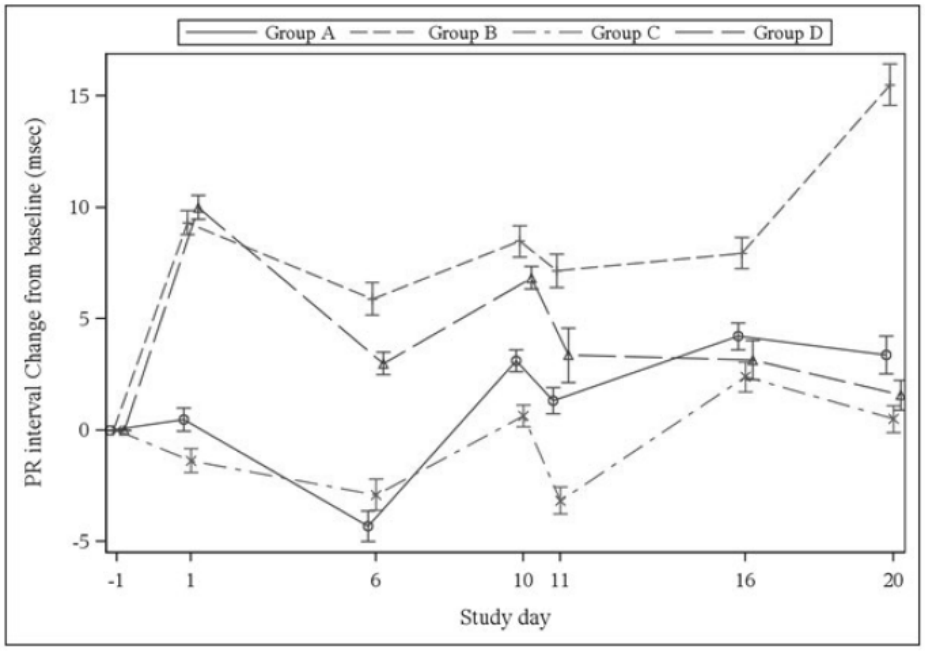


Source: A2116 CSR, Figures 11-8 and 11-10

The changes in the PR interval was analyzed using a mixed-effects ancova model with day, treatment and interaction between day and treatment as fixed effects, average baseline as a covariate and a random effect on subject. The graphical results of the PR interval changes are shown in Figure 3.

Figure 3: Sponsor's analysis of changes in PR for 2.5 h (top row) and 6.5 h (bottom row). Errorbars represent mean +/- SE.



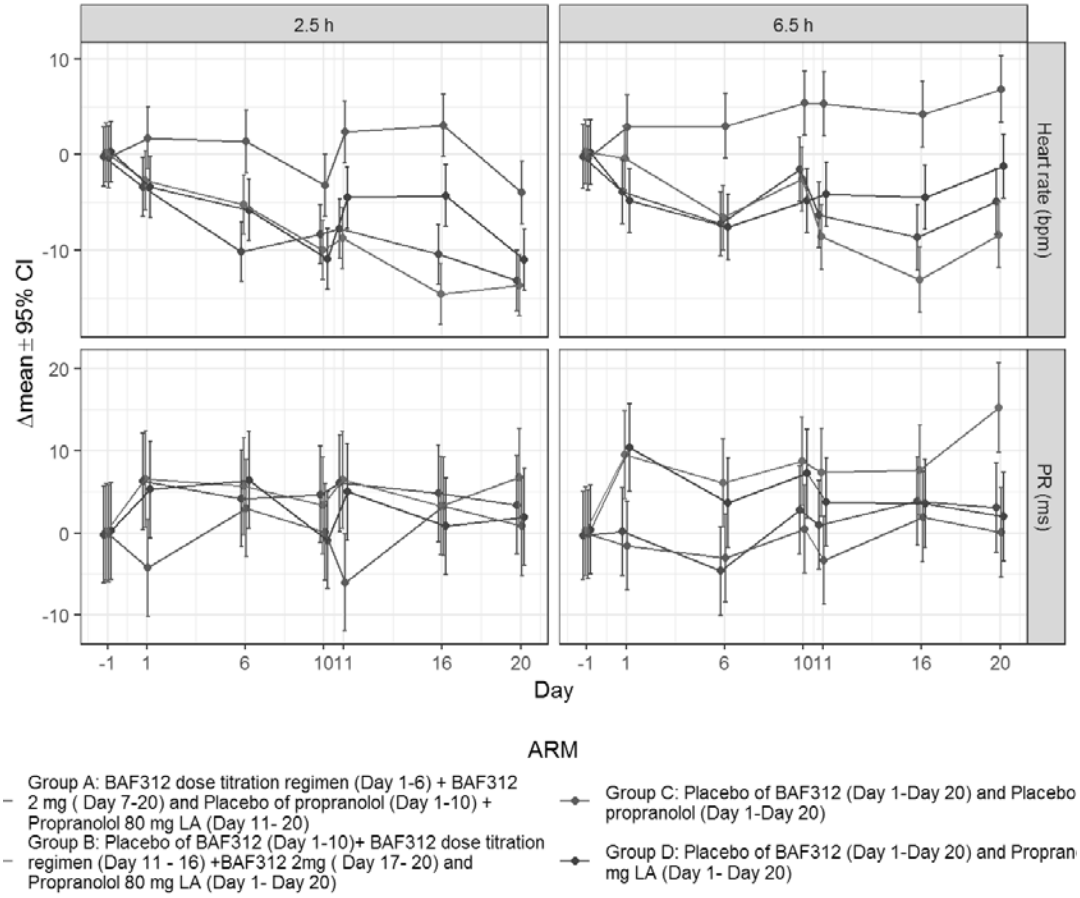


Source: A2116 CSR, Figures 11-5 and 11-6

When analyzing the data submitted with the model described by the sponsor, the reviewer was unable to reproduce the SEs in the figures provided by the sponsor. The SEs in the figure from the sponsor appear to be <1 ms, however, the SEs listed in table 14.2-4.2 are ~3 ms. The SEs listed in the table are comparable to the SEs from the reviewer's analysis.

The results of the reviewer's analysis are shown in Figure 4. This analysis suggests that most of the confidence intervals for the on-treatment data overlap with the placebo. However, the change from baseline for PR at the 6.5 h time-point on day 20 for group B is significantly higher than placebo. This finding is likely a by chance finding given the negative findings at steady-state for a higher dose in the TQT study, absence of significant changes in PR at 2.5 h, no significant findings for group A (siponimod + propranolol compared to B propranolol + siponimod) and no replicate measurements.

Figure 4: Change from baseline at for siponimod + propranolol (A); propranolol + siponimod (B); placebo (C) and propranolol (D). Error bars represent mean +/- 95% confidence interval.



Source: Reviewer's analysis using the ancova model described by the sponsor.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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/s/

LARS JOHANNESEN
12/14/2018

CHRISTINE E GARNETT
12/14/2018

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

NDA	209884
Brand Name	Mayzent
Generic Name	Siponimod (BAF312)
Sponsor	Novartis Pharmaceuticals Corporation
Indication	Secondary Progressive Multiple Sclerosis (SPMS)
Dosage Form	Tablets
Drug Class	Immunomodulator, S1P receptor agonist
Therapeutic Dosing Regimen	• 2 mg QD maintenance dose, preceded by 5-day titration from 0.25 - 1.25 mg • 1 mg QD maintenance dose, (b) (4) in CYP2C9 genotypes *1*3 or *2*3
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	Single MTD: 25 mg (occurrence of symptomatic bradycardia after a single dose of 75 mg). Multiple MTD: 20 mg QD (highest investigated multiple dose over 28 days which was well tolerated, no multiple dose MTD was formally established)
Submission Number and Date	001, 06/28/2018
Review Division	DNP

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1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

A QTc prolongation effect of siponimod (dosed at 2 mg and 10 mg) was detected in the TQT study BAF312A2118. The largest upper bounds of the 2-sided 90% CI for the mean differences between siponimod 2 mg and placebo and between siponimod 10 mg and placebo were 12.8 ms and 12.6 ms, respectively (Table 1); which were above the 10 ms threshold for regulatory concern as described in ICH E14 guidelines. No subject had QTcF>480 ms or ΔQTcF >60 ms. The largest lower bound of the two-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated (Figure 3 and Figure 4), indicating that assay sensitivity was established.

In this randomized, double-blind, placebo- and moxifloxacin-controlled, multiple dose parallel study in 304 healthy adult subjects, siponimod was administered once daily using an up-titration regimen to establish steady state conditions for the clinical therapeutic dose of siponimod 2 mg followed by that for a supratherapeutic dose of 10 mg. Overall summary of findings is presented in Table 1.

Table 1: **The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Siponimod 2 mg and Siponimod 10 mg QD, and the Largest Lower Bound for Moxifloxacin 400 mg (FDA Analysis)**

Treatment	Day	Time (h)	Mean ΔΔQTcF (ms)	90% CI (ms)
Siponimod 2 mg QD	10	3	9.7	(6.6, 12.8)
Siponimod 10 mg QD	18	3	9.3	(6.0, 12.6)
Moxifloxacin 400 mg*	10	4	13.2	(10.0, 16.3)
	18	3	14.1	(10.8, 17.4)

*Multiple endpoin adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4-time points are 8.9 ms and 9.6 ms on Days 10 and 18, respectively.

The supratherapeutic dose (10 mg once daily) of siponimod in this TQT study produces mean C_{max} and AUC values that are 5-fold of that for the highest therapeutic dose of 2 mg once daily. The possible high clinically relevant exposure scenarios for this drug would be CYP2C9 genotype (poor metabolizers) and DDI with CYP2C9/CYP3A4 inhibitor (fluconazole). Siponimod mean C_{max} increased by 21% and 16% and AUC increased by 2- and 4-fold in CYP2C9*2*3 and CYP2C9*3*3 (poor metabolizer) subjects, respectively, as compared to CYP2C9*1*1 (extensive metabolizer) subjects. DDI with fluconazole resulted in 1.1-fold and 2-fold higher C_{max} and AUC, respectively, for siponimod. The 5-fold exposure margin in the TQT study would cover these high clinically relevant exposure scenarios.

Although the primary IUT analysis showed a clinically relevant QTc effect (>10 ms), there was an absence of dose-response relationship for QTc effects and the concentration-QTc analysis with the 5-fold dose/exposure range did not reveal a clear concentration-dependent QTc prolongation signal as well.

1.2 QT INTERDISCIPLINARY REVIEW TEAM'S COMMENTS

- Our results do not agree with the sponsor's conclusion that there was no QT prolongation. The sponsor ignored both the correlation across different timepoints and baseline covariate in the sponsor's primary analysis using ANOVA by each timepoint. We used Mixed effect Model Repeat Measurement (MMRM) which incorporates correlation across different timepoints and baseline adjustment in our independent analysis in Section 5.2.
- The cumulative *in vitro* and clinical data seem to suggest that the QTc effects seen in the study may not be due to any direct effects mediated by inhibition of hERG potassium channel. The design of the study does not allow elucidation of whether the observed effects are delayed effects due to protein trafficking etc., because:

(i) measurement of QTc effects were done directly at steady state and there is no assessment available at 24 h after the first dose in this study;

(ii) the first dose was 0.25 mg (much lower than 2 mg) and even if there were to be measurements after this dose, those may not have been adequate to observe any delayed effects.

In any case, the exposure margin in this TQT study sufficiently covers the high clinically relevant exposure scenarios and we do not believe any W&P language is warranted for the drug based on the current data.

2 PROPOSED LABEL

The following is the sponsor's proposed labeling language for QTc related effects.

12.2 Pharmacodynamics

(b) (4)

7.2 Anti-arrhythmic drugs, QT Prolonging Drugs, Drugs that may Decrease Heart Rate

(b) (4)

The sponsor's proposed labeling above for Section 7.2 is acceptable and we do not have any further edits to this section. The QT-IRT's proposed labeling edits for Section 12.2 are provided below, which are a suggestion only. We defer the final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

In a thorough QT study with therapeutic and supratherapeutic doses of 2 mg and 10 mg siponimod at steady-state, siponimod treatment resulted in a prolongation of QTc, with

the maximum mean (upper bound of two-sided 90% CI) of 9.7 (12.8) ms at 2 mg dose and 9.3 (12.6) ms at 10 mg dose. There was an absence of dose- and exposure-response relationship for QTc effects with the 5-fold dose and exposures achieved by the supratherapeutic dose. No subject had absolute QTcF >480 ms or ΔQTcF >60 ms for siponimod treatment.

Reviewer's comments:

1. *We have modeled our proposal based on labeling language for fingolimod, which is in the same class as siponimod. Siponimod seems to exhibit similar effects which could be drug class related.*
2. (b) (4) *We used Mixed effect Model Repeat Measurement (MMRM) which incorporates correlation across different timepoints and baseline adjustment in our independent analysis.*
3. *We are editing the heading of sub-section to be consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance.*

3 BACKGROUND

3.1 PRODUCT INFORMATION

Siponimod (BAF312) is a novel immunomodulator that selectively targets sphingosine 1-phosphate (S1P) receptor subtypes 1 and 5. It is being developed, as an oral formulation, for the treatment of multiple sclerosis (MS) and will be tested clinically in other autoimmune diseases.

3.2 MARKET APPROVAL STATUS

Siponimod is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

In vitro, siponimod does not significantly inhibit hERG channel currents in HEK293 cells; nonsignificant inhibition of 9% was measured at the maximum concentration tested of 25 μM (12.9 μg/ml) (~2000000-fold higher than the predicted *free* Cmax at multiple doses of 2 mg). Binding affinity to ion channels (Ca L-Type, Na Typ II and K(ATP)) have been evaluated in *in vitro* assays. No relevant potential for inhibition were identified.

In vivo, transient decrease in heart rate was identified in all tested species (rat, rabbit, guinea pig and monkey). No adverse cardiovascular effects or clinically relevant ECG changes were observed in a single-dose GLP safety pharmacology study in monkey up to the maximum tolerated single dose of 150 mg/kg (Cmax: >50 μM). Increases in the QT interval (without correction factor) and a second-degree AV block were identified in 1 monkey in a non-GLP study at the highest dose tested of 100 mg/kg. In repeat dose toxicity studies in monkey, there were no adverse cardiovascular effects or clinically relevant ECG changes noted over an exposure duration of 2, 4, 26 and 52 weeks. Siponimod does not

belong to a chemical/pharmacological class in which some members have been shown to induce QT interval prolongation in humans.

3.4 PREVIOUS CLINICAL EXPERIENCE

No cases of sudden death, Torsade de pointes, ventricular flutter/ventricular fibrillation, or seizures were detected/reported throughout the Clinical Pharmacology program. Episodes of presyncope (N=15) or syncope (N=1) were reported in a total of 16 subjects across different dose levels in the Clinical Pharmacology program, which were considered to be associated with a vasovagal reaction after blood draw and not related to siponimod intake. Asymptomatic episodes of ventricular arrhythmia detected in the Holter ECG and online cardiac monitoring included single ventricular extrasystoles, ventricular couplets, bigeminy and trigeminy, which were observed with similar incidence under siponimod treatment compared to other treatments (placebo and other drugs alone or in combination with siponimod).

An asymptomatic, self-limiting episode of non-sustained ventricular tachycardia of 8 beats (reported as an AE) in one subject receiving a siponimod i.v. infusion of 0.25 mg over 3 h (A2126). Other episodes of non-sustained ventricular tachycardia (not reported as AEs, but detected in Holter ECG recordings), were reported infrequently (N=20 subjects), were asymptomatic, and without evidence of higher incidence under siponimod compared to placebo treatment.

See Appendix 6.1 for more details.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of Siponimod's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 76,112 (see the QT-IRT memos dated 02/15/2012 and 06/13/2012).

The sponsor submitted the study report including descriptive statistics for the study with ECG assessments, electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A randomized, double-blind, parallel-group, placebo- and moxifloxacin-controlled multiple-dose study to assess the QT interval after oral administration of BAF312 in healthy subjects

4.2.2 Protocol Number

BAF312A2118

4.2.3 Study Dates

Study initiation date: 12-Jun-2012 (first subject first visit)

Study completion date: 20-Sep-2012 (last subject last visit)

4.2.4 Objectives

Primary objective: To assess if the placebo-corrected, baseline-adjusted mean QTcF (ΔΔQTcF) at therapeutic and supratherapeutic doses of siponimod exceeds the regulatory threshold level of concern of 5 ms as evidenced by an upper bound of a one-sided 95% CI for the largest mean QTc effect of 10 ms.

Secondary objectives:

- To evaluate the effect of single doses of moxifloxacin on the placebo-corrected, baseline-adjusted mean QTcF (ΔΔQTcF) in healthy subjects to confirm assay sensitivity.
- To evaluate the effect of therapeutic and supratherapeutic doses of siponimod on the QTcI interval compared to placebo, in healthy subjects.
- To assess the safety and tolerability of therapeutic and supratherapeutic doses of siponimod in healthy subjects.
- To evaluate baseline-corrected changes in ECG variables in healthy subjects.
- To evaluate ECG morphologic changes related to cardiac repolarization (ST segment and T waves) in healthy subjects.
- To assess the pharmacokinetics of siponimod (and selected metabolites) at therapeutic and supratherapeutic dose levels in healthy subjects.
- To assess the pharmacokinetics of single doses of moxifloxacin in healthy subjects.
- To explore the PK/PD relationship of siponimod plasma concentrations (and/or PK parameters) and QTcF changes in healthy subjects.

4.2.5 Study Description

4.2.5.1 Design

This was a randomized, double-blind, placebo- and moxifloxacin-controlled, multiple oral dose study conducted in parallel groups of healthy adult male and female subjects.

Siponimod up-titration regimen for Group A, as well as the dose regimen for Group B and C are described as below and in Figure 1. Subjects were assigned to one of the following 3 treatment arms in a ratio of 1:1:1.

Group A (Siponimod group): An up-titration regimen was employed to stepwise establish steady state conditions for the clinical therapeutic dose of siponimod 2 mg (Days 1-10) and a supratherapeutic dose of 10 mg (Days 11-18) during the treatment period from Day 1 to Day 18. Subjects also received Siponimod-placebo on Day -1 and moxifloxacin-placebo on Day 10 and Day 18.

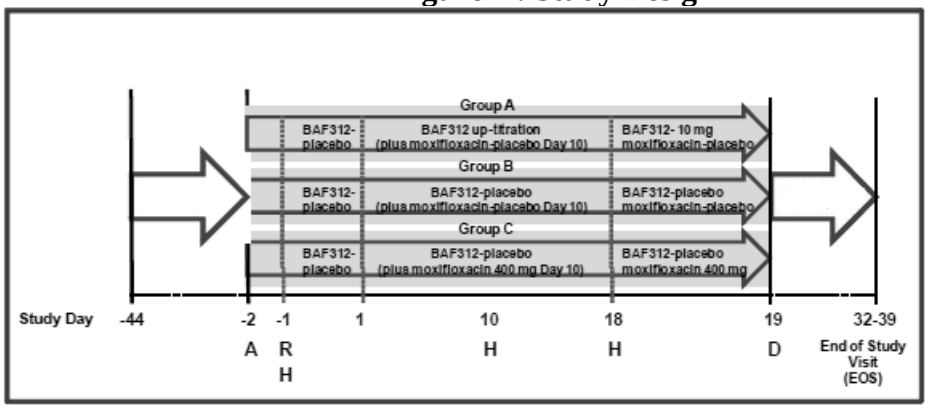
The following dosing schedule was used to gradually uptitrate the dose in this group:

Day	BAF312 (Group A)
-1	BAF312-Placebo
1	0.25 mg
2	0.25 mg
3	0.5 mg
4	0.75 mg
5	1.25 mg
6	2 mg
7	2 mg
8	2 mg
9	2 mg
10	2 mg + Moxifloxacin-Placebo
11	3 mg
12	5 mg
13	8 mg
14	10 mg
15	10 mg
16	10 mg
17	10 mg
18	10 mg + Moxifloxacin-Placebo

Group B (Placebo group): Subjects were administered siponimod-placebo from Days -1 to Day 18. In addition, subjects were co-administered moxifloxacin-placebo on Day 10 and Day 18.

Group C (Moxifloxacin group): Subjects were administered siponimod-placebo on Days -1 to Day 18 and were co-administered single oral doses of 400 mg moxifloxacin on Day 10 and Day 18.

Figure 1 : Study Design



Key: **A**: Admission to clinic for in-subject stay; **D**: Discharge from clinic; **H**: Holter ECG assessment; **R**: Randomization

Source: Study report, Table 9-2.

4.2.5.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

This was a double blinded study.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

See Section 4.2.5.1.

4.2.6.2 Sponsor's Justification for Doses

The mean exposure (AUCtau) for the 10 mg supratherapeutic dose is 4.8-fold higher than at the 2 mg therapeutic dose, whereas the Cmax,ss is approx. 5-fold higher than the 2 mg Cmax,ss. The BAF312 10 mg supratherapeutic dose is therefore appropriate to cover exposure expected in patients receiving the anticipated highest therapeutic dose of 2 mg.

Results of the drug-drug interaction study (CBAF312A2108) with BAF312 and fluconazole (CYP2C9/CYP3A4 inhibitor) showed that AUC of BAF312 was increased by 2-fold. These results suggest that a dose of 10 mg, which is 5-fold the expected therapeutic dose of 2 mg, is also appropriate to cover exposures expected in patients receiving a BAF312 and a concomitant CYP2C9/CYP3A4 inhibiting treatment.

*Reviewer's Comment: The supratherapeutic dose (10 mg once daily) of siponimod in this TQT study produces mean C_{max} and AUC values that are 5-fold of that for the highest therapeutic dose of 2 mg once daily. The possible high clinically relevant exposure scenarios for this drug would be CYP2C9 genotype (poor metabolizers) and DDI with CYP2C9/CYP3A4 inhibitor (fluconazole). Siponimod mean C_{max} increased by 21% and 16% and AUC increased by 2- and 4-fold in CYP2C9*2*3 and CYP2C9*3*3 (poor metabolizer) subjects, respectively, as compared to CYP2C9*1*1 (extensive metabolizer) subjects. DDI with fluconazole resulted in 1.1-fold and 2-fold higher Cmax and AUC, respectively, for siponimod. The 5-fold exposure margin in the TQT study would cover these high clinically relevant exposure scenarios.*

4.2.6.3 Instructions with Regard to Meals

For each subject, the study drug was administered at approximately the same time each day from Day -1 up to and including Day 18. On study Days -1, 10 and 18, study drug was administered following an overnight fast. In addition on these days, subjects were not be given food until 4 h post dose. On all other study days, subjects were given standardized meals, with breakfast being given at least 1 h after dosing.

Reviewer's Comment: Acceptable. Food does not affect Cmax or AUC of the drug.

4.2.6.4 ECG and PK Assessments

ECG and PK were evaluated at pre-dose, and at 0.5, 1, 2, 3, 4, 6, 12, and 24 hours after dose on Day 10 and Day 18.

Reviewer's Comment: Acceptable. The ECG/PK sampling was appropriate to capture effects near Tmax (~4 h) and any delayed effects up to 24 h.

4.2.6.5 Baseline

Sponsor used time-matched QTc values on Day -1 as baselines.

4.2.7 ECG Collection

12-lead Holter ECGs was collected over a 25-h period using validated Holter ECG recorders at 1000 Hz resolution at baseline (Day -1) and during the therapeutic and supratherapeutic profile days on Days 10 and 18 of the treatment period.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 304 subjects were enrolled in this study, of which, 270 completed the study. From the 304 enrolled subjects, 281 were included in the PK, PD and PK/PD analysis sets, with the following number of subjects assigned to treatment groups:

- Moxifloxacin - safety analysis set N=103; PK, PD, PK/PD N=95
- Placebo - safety analysis set N=102; PK, PD, PK/PD N=94
- Siponimod (BAF312) - safety analysis set n=99; PK, PD, PK/PD n=92

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The primary endpoint was time-matched mean difference between siponimod (dosed at 2 mg and 10 mg) and placebo in QTcF. Table 2 presents 2-sided 90% CI between siponimod 2 mg and placebo, and siponimod 10 mg and placebo for each time point.

In a sponsor's analysis, a linear regression model was fitted separately for each time point with the change from baseline being the dependent variable and treatment group the independent variable. The t-test of the coefficient of treatment variable is equivalent to a two-sample t-test. The statistical analysis was carried out using SAS® procedure PROC MIXED statement:

```
proc mixed data=Holter;
by visit time;
class treatment;
model change = treatment /s ;
lsmeans treatment / cl diff=control("Placebo") alpha=0.1;
run;
```

The largest upper bounds of the 2-sided 90% CI for the mean differences in ΔΔQTcF between siponimod 2 mg and placebo, and between siponimod 10 mg and placebo are 9.86 ms and 9.69 ms, respectively (see Table 2). The sponsor concluded there was no significant QT-prolonging potential of siponimod.

Table 2: Sponsor's Analysis of ΔΔQTcF for Siponimod 2 mg and 10 mg

		BAF312 2 mg - Placebo			BAF312 10 mg - Placebo		
Parameter	Hours post dose (h)	Estimated difference	SE	90% CI	Estimated difference	SE	90% CI
QTcF (ms)	0.5	4.34	1.15	(2.44; 6.24)	3.74	1.40	(1.42; 6.05)
	1.0	4.43	1.38	(2.16; 6.71)	6.05	1.47	(3.61; 8.48)
	2.0	6.39	1.32	(4.20; 8.57)	6.63	1.42	(4.28; 8.98)
	3.0	7.83	1.23	(5.80; 9.86)	7.20	1.50	(4.72; 9.69)
	4.0	6.58	1.23	(4.55; 8.61)	5.80	1.56	(3.22; 8.39)
	6.0	6.30	1.26	(4.22; 8.39)	4.89	1.57	(2.30; 7.48)
	12.0	4.19	1.17	(2.24; 6.13)	3.29	1.25	(1.23; 5.35)
	24.0	2.59	1.17	(0.65; 4.54)	4.96	1.37	(2.69; 7.23)

Source: Study report, Table 11-3.

Reviewer's Comments: ANOVA by each timepoint was not appropriate as both the correlation across different timepoints and baseline covariate were ignored in sponsor's analysis. We provided our independent analysis using Mixed effect Model Repeat Measurement (MMRM) which incorporates correlation across different timepoints and baseline adjustment in Section 5.2. Our ΔΔQTcF analysis results show a significant QTc prolonging effect for 2 mg and 10 mg based on baseline-adjusted model while the sponsor's results show no QTc prolonging effect.

4.2.8.2.2 Assay Sensitivity

Reviewer's Comment: Sponsor used the same analysis in assay sensitivity. Both sponsor's results and this reviewer's results conclude that the assay sensitivity is demonstrated in this study. We provide our independent analysis in Section 5.2.

4.2.8.2.3 Categorical Analysis

Reviewer's Comments: We provided our independent analysis in Section 5.2. Our categorical analyses concurred with the sponsor's conclusion - categorical analysis of QTcF outliers did not reveal any subjects with treatment-emergent QTcF values >480 ms nor with QTcF increases from baseline >60 ms.

4.2.8.3 Safety Analysis

There were no deaths reported in this study. Two subjects ([(b) (6)] and [(b) (6)]) were reported with SAEs in this study. Subject [(b) (6)] was in moxifloxacin treatment group and was reported with SAE of atrial fibrillation. Subject [(b) (6)] was from BAF312 treatment arm and was reported with SAE of dengue fever.

Two subjects were discontinued due to adverse events. Subject [(b) (6)] with asymptomatic atrial fibrillation which was classified as an SAE was discontinued from treatment on Day 11 after receiving placebo on Day -1 to Day 9 and one dose of moxifloxacin 400 mg on Day 10. Subject [(b) (6)] was enrolled in BAF312 treatment group and was reported with generalized papular rash.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

C_{max} and AUC values for siponimod (and its metabolites M3 and M5) in this TQT study were approximately 5-fold higher following administration of 10 mg supratherapeutic dose compared with the highest proposed clinical dose of 2 mg (Table 3).

Table 3: PK parameters for Siponimod (BAF312A) and its metabolites M3 and M5 on Day 10 and 18 after administration of 2 mg QD from day 6-10 and 10 mg QD from day 14-18 in healthy volunteers

Siponimod

PK parameter	Day 10 (2 mg)	Day 18 (10 mg)
Cmin,ss# (ng/mL)	16 ± 5.73 [14.5 ; 63] (n=92)	76.4 ± 29.8 [61.2 ; 141.0] (n=89)
Cavg,ss# (ng/mL)	24.1 ± 6.60 [23.2 ; 26.7] (n=75)	116 ± 31.5 [112 ; 30.1] (n=87)
Cmax,ss# (ng/mL)	31.5 ± 8.89 [30.4 ; 27.6] (n=92)	157 ± 39.2 [152 ; 28.3] (n=89)
Tmax* (h)	4.03 (2.02-12.1) (n=92)	4.02 (2.02-6.05) (n=89)
AUCtau,ss# (h*ng/mL)	577 ± 159 [558 ; 26.7] (n=75)	2790 ± 755 [2680 ; 30.1] (n=87)

M3

PK parameter	Day 10 (2 mg)	Day 18 (10 mg)
Cmin,ss# (ng/mL)	8.29 ± 3.68 [7.66; 46.9]	44.3 ± 24.9 [38.3; 79.9]
Cavg,ss# (ng/mL)	11.0 ± 3.24 [10.6 ; 32.1]	63.2 ± 29.3 [57.4 ; 47.4]
Cmax,ss# (ng/mL)	14.8 ± 5.34 [13.9 ; 36.4]	79.8 ± 35.8 [72.8 ; 45.4]
Tmax,ss* (h)	6.03 (2.05 - 12.0)	6.03 (3.02 - 24.0)
AUCtau,ss# (h*ng/mL)	265 ± 77.7 [254 ; 32.1]	1520 ± 704 [1380 ; 47.4]

M5

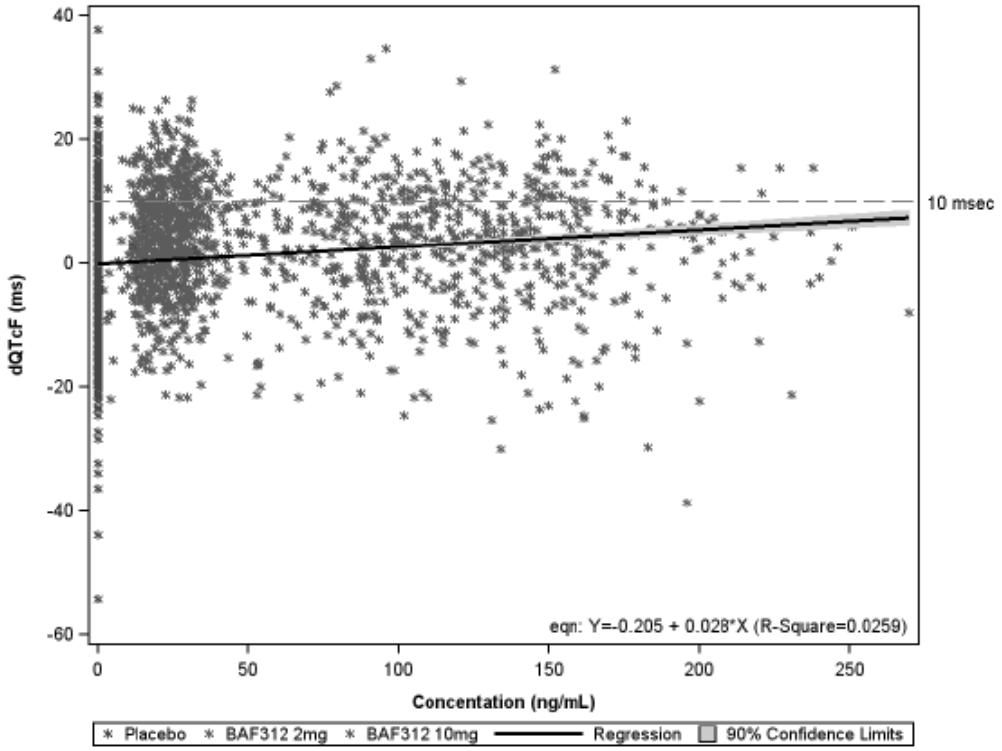
PK parameter	Day 10 (2 mg)	Day 18 (10 mg)
Cmin,ss# (ng/mL)	0.388 ± 0.129 [0.369; 39.8]	1.91 ± 0.780 [1.72 ; 74.7]
Cavg,ss# (ng/mL)	0.554 ± 0.146 [0.535; 27.4]	2.75 ± 0.843 [2.61; 35.0]
Cmax,ss# (ng/mL)	0.720 ± 0.200 [0.692; 29.6]	3.63 ± 1.13 [3.44; 35.0]
Tmax,ss* (h)	4.03 (2.02 – 12.1)	4.03 (3.02 – 24.0)
AUCtau,ss# (h*ng/mL)	13.3 ± 3.49 [12.8; 27.4]	66.1 ± 20.2 [62.7; 35.0]

Source: CSR for Study BAF312A2118, Table 11-17; CSR addendum 1, Table 2-1 and Table 2-2

4.2.8.4.2 Exposure-Response Analysis

Concentration-response analysis revealed a positive correlation between the BAF312 plasma concentration and the time-matched change from baseline in QTcF (ΔQTcF) characterized by a regression line with the following equation: y = -0.205 + 0.028*x. The slope of the curve of 0.028 was small and the upper bound of the 90% confidence band (grey area) remained below 10 ms within the investigated exposure range (r^2=0.0259).

Figure 2: Concentration response for time-matched change from baseline in QTcF versus concentration for siponimod and regression line with two-sided 90% confidence bands



Source: CSR for Study BAF312A2118, Figure 11-12

Reviewer's comments: The QT-IRT had recommended the sponsor to adjust for effect of placebo on QT for exposure-response analysis in order to predict population average ΔΔQTc and its corresponding confidence interval at appropriate concentrations of interest. The sponsor did not compute the ΔΔQTc as per our recommendation. Nevertheless, it is clear from the data that characterizing the QTc effects using a direct effect C-QTc model may not be appropriate in this case (see reviewer's analysis in Section 5.3).

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF and QTcI for their primary analyses, which are acceptable since no large changes in heart rate were observed, i.e., mean changes ≤ 10 bpm (section 5.2.2). Therefore, no assessment of the QT/RR correction methodology is necessary and QTcF was used for the reviewer's analyses.

5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for Siponimod

The statistical reviewer used Mixed effect Model Repeat Measurement (MMRM) which incorporates correlation across different timepoints and baseline adjustment. The results are presented in Table 4. The model includes treatment, time, and treatment interaction as fixed effect and baseline values as a covariate. The largest upper bounds of the 2-sided 90% CI for the mean differences in ΔΔQTcF between siponimod 2 mg and placebo, and between siponimod 10 mg and placebo are 12.8 ms and 12.6 ms, respectively.

Table 4: Analysis Results of ΔQTcF and ΔΔQTcF for Siponimod 2 mg and 10 mg

			Treatment Group		
		Placebo	BAF312		
		ΔQTcF	ΔQTcF	ΔΔQTcF	
Day	Time (h)	LS Mean	LS Mean	LS Mean	90% CI
10	0.5	-3.4	3.1	6.5	(3.5, 9.5)
	1	-2.7	4.3	6.9	(3.8, 10.1)
	2	-1.8	6.7	8.5	(5.3, 11.6)
	3	-1.7	8.0	9.7	(6.6, 12.8)
	4	-1.9	7.6	9.6	(6.4, 12.7)
	6	-4.6	4.5	9.2	(6.4, 12.0)
	12	-3.7	3.5	7.2	(4.3, 10.0)
	24	-1.0	4.6	5.5	(2.7, 8.4)
18	0.5	-3.9	2.2	6.1	(2.8, 9.3)
	1	-4.3	4.6	8.9	(5.6, 12.1)
	2	-3.3	5.5	8.8	(5.5, 12.0)
	3	-2.8	6.5	9.3	(6.0, 12.6)
	4	-3.2	5.6	8.9	(5.5, 12.2)
	6	-6.5	1.5	8.1	(5.0, 11.1)
	12	-4.1	2.6	6.6	(3.7, 9.6)
	24	-5.0	2.8	7.9	(4.6, 11.1)

5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data as was used to analyze QTc data. The results are presented in Table 5. The largest unadjusted 2-sided 90% lower confidences intervals are 10.0 ms and 10.8

ms at doses of 2 mg and 10 mg, respectively. By considering Bonferroni multiple endpoint adjustments, the largest lower confidence intervals are 8.9 ms and 9.6 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin could be detected from the study.

Table 5: Analysis Results of ΔQTcF and ΔΔQTcF for Moxifloxacin 400 mg

			Treatment Group			
		Placebo	Moxifloxacin 400 mg			
		ΔQTcF	ΔQTcF	ΔΔQTcF		
Day	Time (h)	LS Mean	LS Mean	LS Mean	90% CI	*Adj. 90% CI
10	0.5	-3.4	5.8	9.2	(6.2, 12.2)	(5.2, 13.3)
	1	-2.7	10.0	12.7	(9.5, 15.8)	(8.4, 16.9)
	2	-1.8	11.0	12.8	(9.6, 15.9)	(8.4, 17.1)
	3	-1.7	11.3	13.0	(9.9, 16.1)	(8.7, 17.3)
	4	-1.9	11.2	13.2	(10.0, 16.3)	(8.9, 17.4)
	6	-4.6	4.7	9.4	(6.6, 12.2)	(5.5, 13.2)
	12	-3.7	5.1	8.8	(6.0, 11.7)	(4.9, 12.7)
	24	-1.0	6.0	6.9	(4.1, 9.8)	(3.1, 10.8)
18	0.5	-3.9	5.4	9.3	(6.1, 12.6)	(4.9, 13.7)
	1	-4.3	9.7	14.0	(10.7, 17.2)	(9.6, 18.3)
	2	-3.3	9.8	13.1	(9.8, 16.3)	(8.6, 17.5)
	3	-2.8	11.3	14.1	(10.8, 17.4)	(9.6, 18.6)
	4	-3.2	10.9	14.1	(10.8, 17.5)	(9.5, 18.7)
	6	-6.5	4.6	11.1	(8.1, 14.2)	(7.0, 15.3)
	12	-4.1	5.9	10.0	(7.0, 13.0)	(6.0, 14.1)
	24	-5.0	4.1	9.1	(5.9, 12.3)	(4.7, 13.5)

*: Bonferroni method was applied for multiple adjustments for 4-time points.

Reviewer's Comment: the lower bounds crossed above 5 ms. Overall, assay sensitivity was demonstrated.

5.2.1.3 Graph of ΔΔQTcF Over Time

Figure 3 and Figure 4 display the time profiles of ΔΔQTcF for different treatment groups.

Figure 3: Mean and 90% CI ΔΔQTcF Time Course for Siponimod 2 mg and Moxifloxacin 400 mg

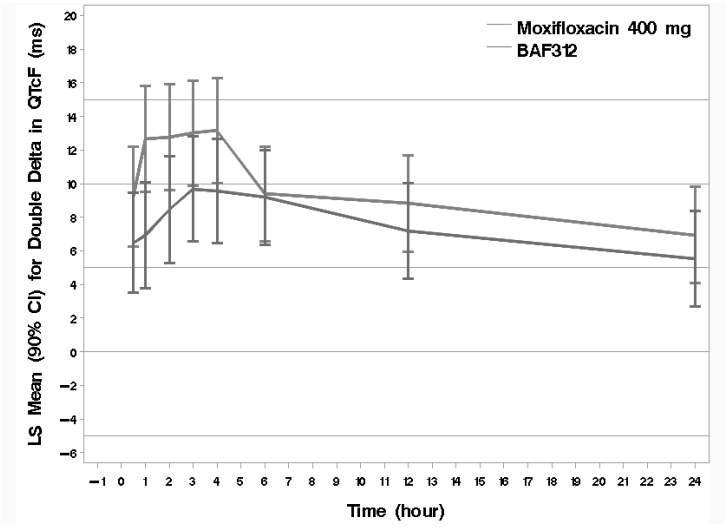
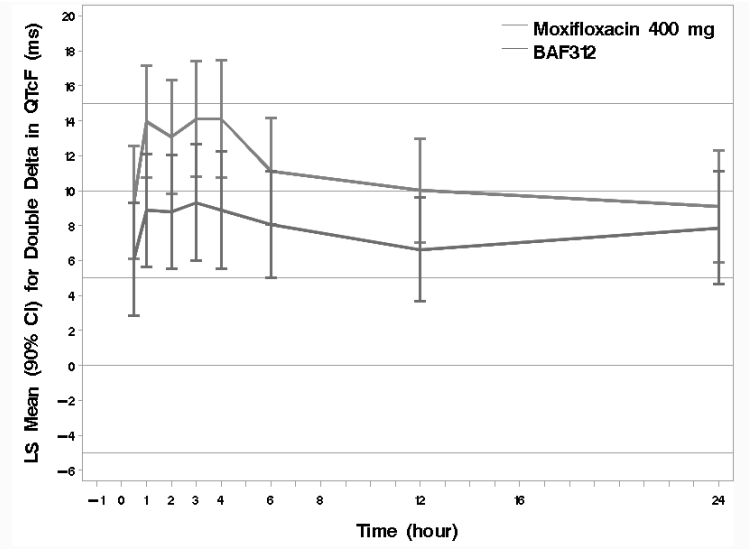


Figure 4: Mean and 90% CI ΔΔQTcF Time Course for Siponimod 10 mg and Moxifloxacin 400 mg



5.2.1.4 Categorical Analysis

Table 6 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms and between 450 ms and 480 ms. No subject's QTcF in Siponimod group is above 480 ms.

Table 6: Categorical Analysis for QTcF

		Total (n)		Value<=450 ms		450 ms<Value<=480 ms	
Dose	**Treatment Group**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**
2 mg	Siponimod	92	735	92 (100%)	735 (100%)	0 (0.0%)	0 (0.0%)
	Placebo	92	731	92 (100%)	731 (100%)	0 (0.0%)	0 (0.0%)
	Moxifloxacin 400 mg	92	732	90 (97.8%)	724 (98.9%)	2 (2.2%)	8 (1.1%)
10 mg	Siponimod	90	713	89 (98.9%)	712 (99.9%)	1 (1.1%)	1 (0.1%)
	Placebo	91	715	90 (98.9%)	714 (99.9%)	1 (1.1%)	1 (0.1%)
	Moxifloxacin 400 mg	91	724	89 (97.8%)	719 (99.3%)	2 (2.2%)	5 (0.7%)

Table 7 lists the number of subjects' changes from baseline QTc ≤30 ms and between 30 and QTc 60 ms. No subject's ΔQTcF in Siponimod group is above 60 ms.

Table 7: Categorical Analysis of ΔQTcF

		Total (n)		Value<=30 ms		30 ms<Value<=60 ms	
Dose	**Treatment Group**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**
2 mg	Siponimod	92	732	92 (100%)	732 (100%)	0 (0.0%)	0 (0.0%)
	Placebo	92	728	91 (98.9%)	727 (99.9%)	1 (1.1%)	1 (0.1%)
	Moxifloxacin 400 mg	92	728	87 (94.6%)	718 (98.6%)	5 (5.4%)	10 (1.4%)
10 mg	Siponimod	90	710	88 (97.8%)	707 (99.6%)	2 (2.2%)	3 (0.4%)
	Placebo	91	713	90 (98.9%)	712 (99.9%)	1 (1.1%)	1 (0.1%)
	Moxifloxacin 400 mg	91	719	84 (92.3%)	710 (98.7%)	7 (7.7%)	9 (1.3%)

Reviewer's comments: The reviewer's analysis confirmed the sponsor's results that no subject with QTcF>480 ms nor ΔQTcF>60 ms at any time point.

5.2.2 HR Analysis

The point estimates of the placebo-corrected mean change from baseline in HR with 90% confidence intervals are presented in Table 8. The change from baseline in HR for siponimod 2 mg was reduced as compared to the placebo at every time point with a maximum reduction of 7.3 bpm 6 hours after dosing. However, the change from baseline in HR for siponimod 10 mg was increased at every time point except 6 hours after dosing as compared to the placebo with a maximum increase of 2.6 bpm 24 hours after dosing.

The larges upper bounds of the 2-sided 90% CI for the mean differences in ΔΔHR between siponimod 10 mg and placebo is 4.5 bpm 24 hours after dosing. Table 9 presents the categorical analysis of HR. One subject experienced HR>100 bpm in the Siponimod 10 mg group.

Table 8: Analysis Results of ΔΔHR and ΔΔHR for Siponimod 2 mg and 10 mg

			Treatment Group		
		Placebo	BAF312		
		ΔHR	ΔHR	ΔΔHR	
Day	Time (h)	LS Mean	LS Mean	LS Mean	90% CI
10	0.5	3.6	0.4	-3.2	(-4.8, -1.5)
	1	2.6	0.3	-2.3	(-3.9, -0.7)
	2	3.1	-0.9	-4.0	(-5.7, -2.3)
	3	3.0	-0.8	-3.8	(-5.5, -2.1)
	4	2.7	-1.0	-3.7	(-5.3, -2.1)
	6	10.6	3.3	-7.3	(-9.4, -5.3)
	12	9.7	5.3	-4.4	(-6.4, -2.5)
	24	3.8	0.4	-3.5	(-5.2, -1.8)
18	0.5	4.3	6.1	1.8	(-0.2, 3.7)
	1	3.8	6.0	2.2	(0.3, 4.1)
	2	4.1	5.4	1.3	(-0.6, 3.2)
	3	3.9	5.1	1.2	(-0.7, 3.0)
	4	4.7	6.1	1.5	(-0.5, 3.4)
	6	12.4	12.2	-0.2	(-2.5, 2.0)
	12	11.1	11.6	0.5	(-1.5, 2.5)
	24	6.4	8.9	2.6	(0.7, 4.5)

Table 9: Categorical Analysis of HR

		Total N		Value<=100 bpm		Value>100 bpm	
Dose	Treatment Group	# Subj.	# Obs.	# Subj.	# Subj.	# Obs.	# Subj.
2 mg	Siponimod	92	735	92 (100%)	735 (100%)	0 (0.0%)	0 (0.0%)
	Placebo	92	731	92 (100%)	731 (100%)	0 (0.0%)	0 (0.0%)
	Moxifloxacin 400 mg	92	732	90 (97.8%)	730 (99.7%)	2 (2.2%)	2 (0.3%)
10 mg	Siponimod	90	713	89 (98.9%)	712 (99.9%)	1 (1.1%)	1 (0.1%)

		Total N		Value<=100 bpm		Value>100 bpm	
Dose	**Treatment Group**	**# Subj.**	**# Obs.**	**# Subj.**	**# Subj.**	**# Obs.**	**# Subj.**
	Placebo	91	715	89 (97.8%)	713 (99.7%)	2 (2.2%)	2 (0.3%)
	Moxifloxacin 400 mg	91	724	87 (95.6%)	719 (99.3%)	4 (4.4%)	5 (0.7%)

5.2.3 PR Analysis

The point estimates of the placebo-corrected mean change from baseline in PR with 90% confidence intervals are presented in Table 10. The largest upper bounds of the 2-sided 90% CI for the mean differences in ΔΔPR between siponimod 2 mg and placebo, and between siponimod 10 mg and placebo are 4.4 ms and 3.5 ms, respectively. No subject experienced PR>200 ms in the Siponimod group.

Table 10: Analysis Results of ΔPR and ΔΔPR for Siponimod 2 mg and 10 mg

			Treatment Group		
		Placebo	BAF312		
		ΔPR	ΔPR	ΔΔPR	
Day	**Time (h)**	**LS Mean**	**LS Mean**	**LS Mean**	**90% CI**
10	0.5	3.2	2.8	-0.4	(-4.0, 3.3)
	1	3.0	1.9	-1.1	(-4.7, 2.4)
	2	2.0	1.1	-1.0	(-4.5, 2.6)
	3	1.7	1.0	-0.7	(-4.3, 2.9)
	4	1.1	0.9	-0.2	(-3.8, 3.4)
	6	-1.1	-0.2	0.9	(-2.5, 4.4)
	12	-1.9	-2.7	-0.8	(-4.3, 2.6)
	24	2.3	3.0	0.7	(-2.9, 4.3)
18	0.5	4.9	1.8	-3.1	(-6.5, 0.3)
	1	3.9	0.6	-3.3	(-6.7, 0.1)
	2	4.5	-0.1	-4.6	(-7.9, -1.4)
	3	4.3	1.1	-3.1	(-6.5, 0.3)
	4	3.2	-0.3	-3.5	(-6.9, -0.1)
	6	0.0	0.2	0.2	(-3.1, 3.5)
	12	-0.6	-0.5	0.1	(-3.0, 3.3)
	24	2.1	0.1	-2.0	(-5.4, 1.4)

5.2.4 QRS Analysis

The point estimates and the 90% confidence intervals are presented in Table 11. The largest upper bounds of the 2-sided 90% CI for the mean differences in ΔΔQRS between siponimod 2 mg and placebo, and between siponimod 10 mg and placebo are 0.5 ms and 0.8 ms, respectively. Table 12 presents the categorical analysis of QRS. Twenty-two subjects and 20 subjects experienced QRS>110 ms in the Siponimod group on Days 10 and 18, respectively.

Table 11: Analysis Results of ΔQRS and ΔΔQRS for Siponimod 2 mg and 10 mg

		Treatment Group			
		Placebo	BAF312		
		ΔQRS	ΔQRS	ΔΔ QRS	
Day	Time (h)	LS Mean	LS Mean	LS Mean	90% CI
10	0.5	0.2	-0.3	-0.5	(-1.4, 0.3)
	1	0.3	-0.3	-0.6	(-1.4, 0.3)
	2	0.2	-0.4	-0.6	(-1.5, 0.3)
	3	0.3	-0.4	-0.6	(-1.5, 0.2)
	4	0.2	-0.2	-0.4	(-1.3, 0.5)
	6	0.2	-0.4	-0.6	(-1.5, 0.3)
	12	-0.1	-0.6	-0.5	(-1.3, 0.3)
	24	0.1	-0.4	-0.5	(-1.4, 0.4)
18	0.5	0.3	0.1	-0.2	(-1.0, 0.6)
	1	0.3	0.2	-0.2	(-1.0, 0.7)
	2	0.2	-0.0	-0.2	(-1.1, 0.6)
	3	0.2	-0.0	-0.2	(-1.1, 0.6)
	4	0.3	0.1	-0.2	(-1.1, 0.6)
	6	0.2	-0.1	-0.3	(-1.2, 0.6)
	12	0.2	0.0	-0.1	(-1.0, 0.8)
	24	0.3	0.2	-0.1	(-1.0, 0.7)

Table 12: Categorical Analysis of QRS

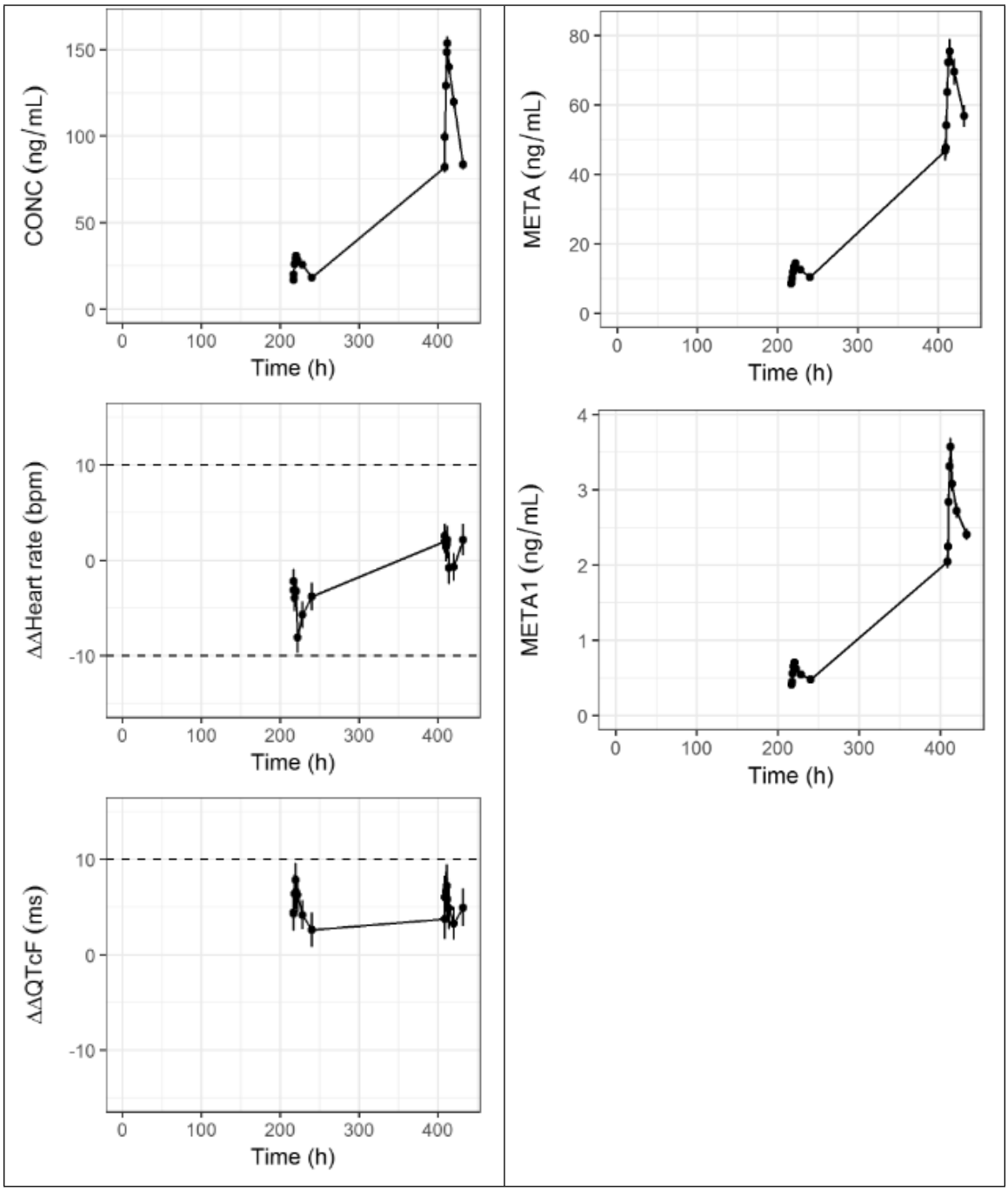
		Total N		Value<=100 ms		100 ms<Value<=110 ms		Value>110 ms	
Dose	**Treatment Group**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**
2 mg	Siponimod	92	735	20 (21.7%)	193 (26.3%)	50 (54.3%)	403 (54.8%)	22 (23.9%)	139 (18.9%)
	Placebo	92	731	13 (14.1%)	148 (20.2%)	59 (64.1%)	449 (61.4%)	20 (21.7%)	134 (18.3%)
	Moxifloxacin 400 mg	92	732	10 (10.9%)	157 (21.4%)	58 (63.0%)	435 (59.4%)	24 (26.1%)	140 (19.1%)
10 mg	Siponimod	90	713	14 (15.6%)	159 (22.3%)	56 (62.2%)	414 (58.1%)	20 (22.2%)	140 (19.6%)
	Placebo	91	715	11 (12.1%)	134 (18.7%)	57 (62.6%)	444 (62.1%)	23 (25.3%)	137 (19.2%)
	Moxifloxacin 400 mg	91	724	14 (15.4%)	165 (22.8%)	53 (58.2%)	401 (55.4%)	24 (26.4%)	158 (21.8%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The objective of the clinical pharmacology analysis is to assess the relationship between drug concentration and ΔQTcF. Prior to evaluating the relationship using a prespecified linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) no delay between plasma concentration and ΔQTcF and 3) absence of non-linear relationship.

An evaluation of the time-course of parent drug (siponimod) and metabolites (M3 and M5) concentrations and changes in ΔΔHR and ΔΔQTcF is shown in Figure 5. The figure shows an absence of significant changes in HR (>10 bpm). But, a reduction in heart rate by ~8 bpm after the 2 mg dose on Day 10 was observed in the data. However, such reduction in HR was not observed after 10 mg dose on Day 18. The information in the summary of safety and similar observations seen in fingolimod (an approved drug belonging to same drug class) seem to suggest that such heart rate reduction effect is more prominent during initiation of treatment for this class of drugs. The mean QTc effects were similar at the two different dose levels evaluated even though the higher (supratherapeutic) dose level was 5-fold of the lower (therapeutic) dose and had also resulted in 5-fold higher concentrations for siponimod as well as M3 and M5 metabolites (Table 3). Thus, clearly there was a lack of dose-response and exposure-response relationship for the observed QTc effects for any of the measured species (parent drug and M3 and M5 metabolites). There did not seem to be any systematic delay between PK and QTc effects.

Figure 5: Time course of parent drug siponimod (CONC) and metabolites M3 (META) and M5 (META1) concentrations, heart rate and QTcF effects



The relationship between drug concentration and ΔQTcF was evaluated to determine if a linear model would be appropriate. Figure 6 shows an apparent non-linearity between siponimod concentration and ΔQTcF suggesting that a linear model will not be appropriate for characterization of this data. An exploratory analysis using the white

paper recommended prespecified linear direct effect model showed a high positive intercept and no slope for the C-QTc relationship. The data was also not amenable for non-linear model because there was no data at lower concentrations (or corresponding to low QTc effects) to inform the relationship. Thus, only the observed data is visualized in Figure 7 along with a smoothened loess curve.

Overall, the cumulative non-clinical and clinical data seem to suggest that the QTc effects seen in the study may not be due to any direct effects mediated by inhibition of hERG potassium channel. The design of the study does not allow elucidation of whether the observed effects are delayed effects due to protein trafficking etc., because:

(i) measurement of QTc effects were done directly at steady state and there is no assessment available at 24 h after the first dose in this study;

(ii) the first dose was 0.25 mg (much lower than 2 mg) and even if there were to be measurements after this dose, those may not have been adequate to observe any delayed effects.

Figure 6: Assessment of linearity of concentration-QTc relationship for Siponimod (BAF312) concentration

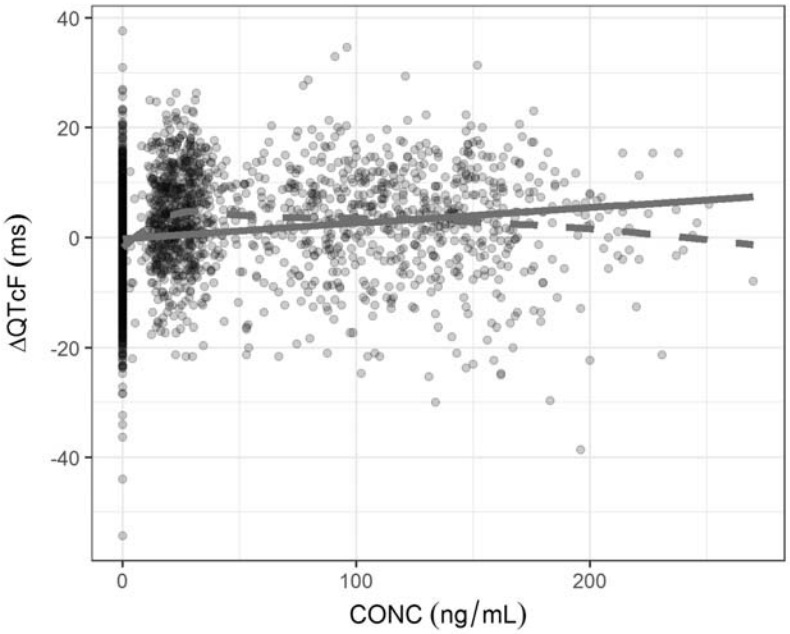
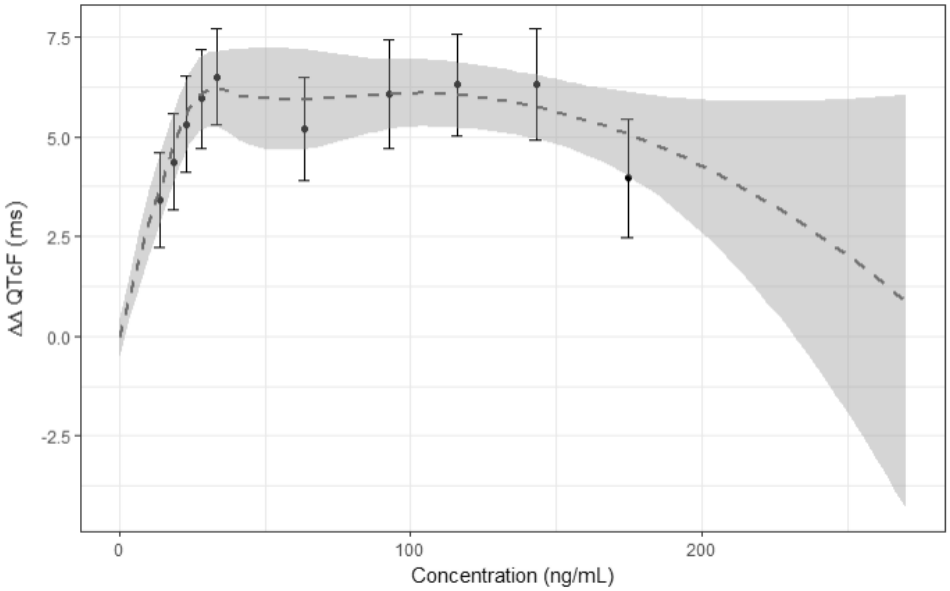


Figure 7: ΔΔQTcF vs. Siponimod (BAF312) concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.

5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

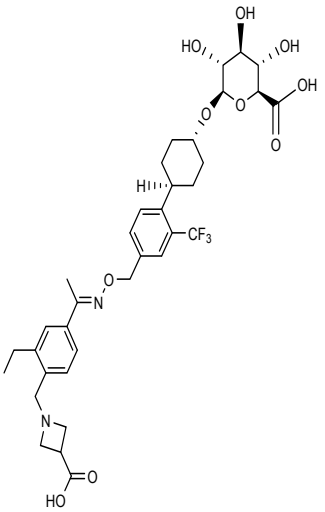
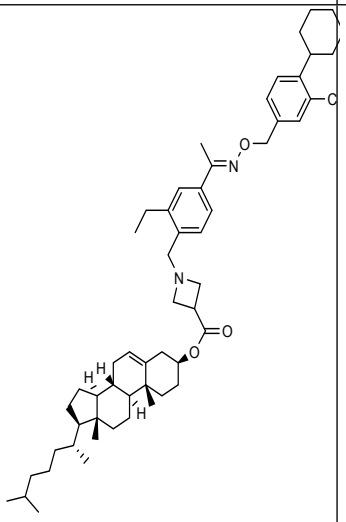
5.4.3 PR and QRS Interval

No clinically meaningful effects on PR and QRS intervals were detected.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose and exposure	• 2 mg q.d. maintenance dose, preceded by 5-day titration from 0.25 – 1.25 mg in CYP2C9 genotypes *1*1, *1*2 and *2*2 • 1 mg q.d. maintenance dose, [redacted] (b) (4) in CYP2C9 genotypes *1*3 and *2*3 to adjust for the respective reduced apparent metabolic clearance compared to CYP2C9*1*1 patients Mean (%CV) Cmax and AUC at the single maximum proposed clinical dose: A single dose of 2 mg was not investigated. The Cmax and AUC of the closest single dose of 2.5 mg are: Geometric Mean Cmax = 19.3 ng/mL (%CV Geometric Mean: 19) Geometric Mean AUCinf = 745 ng/mL*h (%CV Geometric Mean: 25) Mean (%CV) Cmax and AUC at the steady state with the maximum proposed clinical dosing regimen (2 mg q.d.): Geometric Mean Cmax,ss = 30.4 ng/mL (%CV Geometric Mean: 27.6) Geometric Mean AUCtau,ss = 558 ng/mL*h (%CV Geometric Mean: 26.7)	
Maximum tolerated dose	Single maximum tolerated dose (MTD):	25 mg (occurrence of symptomatic bradycardia after a single dose of 75 mg).
	Multiple maximum tolerated dose (MTD):	20 mg q.d. (highest investigated multiple dose over 28 days which was well tolerated, no multiple dose MTD was formally established).
Principal adverse events	In pooled AE analyses from single and multiple doses studies of siponimod in healthy subjects the 3 most frequent AEs were headache (32.5% and 20.8%, respectively), dizziness (12.1% and 5.7%, respectively) and nausea (5.5% and 4.2%, respectively). Dose limiting adverse event were represented by occurrence of symptomatic bradycardia at single doses of 75 mg.	
Maximum dose tested	Single Dose	75 mg
	Multiple Dose	20 mg q.d. over 28 days
Exposures Achieved at Maximum Tested Dose	Single Dose	Geometric Mean Cmax = 491 ng/mL (%CV Geometric Mean: 51) Geometric Mean AUCinf = 18600 ng/mL*h (%CV Geometric Mean: 51)
	Multiple Dose	Geometric Mean Cmax,ss = 359 ng/mL (%CV Geometric Mean: 17) Geometric Mean AUCtau,ss = 6370 ng/mL*h (%CV Geometric Mean: 23)

Range of linear PK	0.1 to 75 mg single dose and 0.3 to 20 mg multiple once daily doses			
Accumulation at steady state	Accumulation calculated using Day 1 and Day 28 data for the dose range 0.3 to 20 mg q.d.: Geometric mean 1.88-2.72 (%CV: 12-47)			
Metabolites	Major human systemic metabolites:			
	Abbreviation	Structure	Occurrence	Pharmacological activity
	M3 (LNL925)	 (hydroxylation, glucuronidation)	plasma (major), urine	No Pharmacological activity
	M17 (LYS815)	 (cholesterol ester formation)	plasma (major)	Negligible contribution to pharmacological activity
Absorption	Absolute/Relative Bioavailability	AUC ratio oral/iv: Geometric mean: 0.84 (%CV 8.6); oral and iv single dose of 0.25 mg		
	Tmax	**For Siponimod** • Median: 4 h (range: 2-12 h) (at 2 mg q.d.) **For major human systemic metabolites:** • Median: 6 h (range: 2-12 h) for metabolite M3 (at 2 mg q.d.)		

		• Median: 96 h (range: 6-144 h) for metabolite M17 (at 0.25 mg single dose)
Distribution	Vd/F or Vd	Vd/F: Geometric Mean: 143 L (% CV: 20)
	% bound	Very plasma protein binding with mean fraction bound: 99.998% (%CV: 0.002)
Elimination	Route	Siponimod was eliminated mainly by metabolism, and subsequent biliary/fecal excretion. • Fecal excretion: 87% (SD: 2.29%, %CV: 2.29*100/87= 2.63%) of the dose (mainly metabolites, only 9.2% siponimod*) • Renal excretion: 3.71% (SD: 0.352%, %CV: 0.352*100/3.71= 9.48%) of the dose as metabolites (siponimod was not detected) *(likely unabsorbed material after oral dose)
	Terminal t½	**For siponimod:** • Geometric mean: 27-57 h (%CV:12-38) for siponimod (at 0.1-75 mg single dose) • Effective T1/2 (based on drug accumulation at steady state) ranged between 22 and 36 hours (at 0.3-20 mg q.d.) **For major human systemic metabolites:** • Geometric mean: 32,9 h (%CV: 18.3) for metabolite M3 (at 0.25 mg single dose) • Geometric mean: 155 h (%CV: 22) for metabolite M17 (at 0.25 mg single dose)
	CL/F or CL	• CL/F Geometric mean: 3.06-3.89 L/h (%CV: 16-45) • In two PopPK analyses in healthy subjects and in MS patients, the typical CL/F value was 3.11 to 3.15 L/h.
Intrinsic Factors	Age	• There was no study conducted in elderly or in pediatric subjects. • The results of two PopPK analyses in healthy subjects and in MS patients did not identify age (range assessed: 18 to 61 years) as a covariate affecting siponimod CL/F.
	Sex	The results of two PopPK analyses in healthy subjects and in MS patients suggest that gender had no significant impact on these siponimod PK parameters.
	Race	Two PopPK analyses in healthy subjects and in MS patients suggest that race/ethnicity does not significantly affect siponimod PK.
	Hepatic & Renal Impairment	• **Hepatic Impairment**: mean siponimod Cmax increased by 16% for the mild impairment group and decreased by approximately 13% and 16% for the moderate and severe impairment groups, respectively. Mean AUC increased by 5% for the mild impairment group and 15% for the severe impairment group, and a decrease in the mean AUC of about

		13% were observed in the moderate impairment group. The unbound siponimod PK parameters were comparable in subjects with mild and moderate hepatic impairment with a trend for a higher unbound AUC (50%) in subjects with severe hepatic impairment. • **Renal Impairment**: a slightly lower Cmax (8%) and a 23% to 24% increase in AUC in severe renal impaired subjects were observed compared to healthy matched subjects. Similar mean Cmax of unbound siponimod was observed for severe renal impairment subjects and matched healthy subjects. Mean unbound AUC increased by 33% in severe renal impairment subjects compared to healthy matched subjects.
	Body weight	Body weight was shown to influence siponimod CL/F and Vc/F in two PopPK analyses in healthy subjects and in MS patients. Subjects with a body weight of 40 and 142 kg have a 53% higher and 40% lower exposure, respectively, compared to subjects with a body weight of 70.5 kg.
	CYP2C9 genotype	CYP2C9 genotype influences siponimod CL/F. Two PopPK analyses indicated that CYP2C9*1*1 and *1*2 subjects behave as extensive metabolizers, *2*2 and *1*3 subjects as intermediate metabolizers and *2*3 and *3*3 subjects as poor metabolizers. Compared to CYP2C9*1*1 subjects, individuals with the CYP2C9*2*2, *1*3, *2*3, and *3*3 genotypes have 20%, 35%-38%, 45%-48%, and 74% smaller CL/F values, respectively. The siponimod exposure is therefore approximatively 25%, 61%, 91%, and 284% higher in CYP2C9*2*2, *1*3, *2*3, and *3*3 subjects, respectively, as compared to *1*1 subjects.
Extrinsic Factors	Drug interactions	• Co-administration of rifampin (a strong CYP3A4/moderate CYP2C9 inducer) in CYP2C9*1*1 subjects: siponimod Cmax and AUC decreased by 45% and 57%. • Co-administration with fluconazole (a moderate CYP3A4/CYP2C9 inhibitor) in CYP2C9*1*1 subjects: siponimod AUC increased by approximately 2-fold increased, apparent terminal T1/2 prolonged by 2-fold. Cmax increased by 10%. • Co-administration with itraconazole (a strong CYP3A4 inhibitor) in CYP2C9*1*2 and CYP2C9*1*3 subjects: decrease in siponimod AUC by 9% to 10% and 24%, respectively, unchanged Cmax.
	Food Effects	High-fat breakfast (0.25 and 4 mg single dose): Cmax and AUC unchanged, Tmax delayed by 2-3 h.
Expected High Clinical Exposure Scenario	The CYP2C9 genotype and the body weight have been identified as relevant predictors of siponimod PK. No dose adjustment is proposed for CYP2C9*2*2 subjects considering their only slightly higher predicted systemic exposure compared to *1*1 subjects (25 %).	

	Under the proposed genotype-based dosing recommendations, a maximum of 2.7-fold exposure increase is predicted for CYP2C9*2*2 subjects in presence of moderate CYP2C9/CYP3A4 inhibitors. A CYP2C9*2*2 patient with a low body weight of 40 kg receiving a moderate CYP2C9/CYP3A4 inhibitors (fluconazole) with a 2 mg q.d. dose of siponimod is expected to exhibit a 5.2-fold (1.25 x 1.53 x 2.7-fold) higher exposure compared to a 70.5 kg CYP2C9*1*1 subject receiving a 2 mg qd dose of siponimod without co-administration of any CYP2C9/CYP3A4 perpetrator drug. The siponimod exposure reached under this expected scenario is therefore predicted to be comparable to the exposure observed following a 10 mg q.d. supratherapeutic dose administration.
Preclinical Cardiac Safety	Non-clinical cardiovascular safety studies with siponimod have been performed under GLP following S7B guidance. Supplementary non-GLP *in vitro*, *ex vivo* and *in vivo* investigative studies were conducted as well. *In vitro,* siponimod does not significantly inhibit hERG channel currents in HEK293 cells; nonsignificant inhibition of 9% was measured at the maximum concentration tested of 25 µM (12.9 µg/ml) (~2000000-fold higher than the predicted *free* Cmax at multiple doses of 2 mg). Binding affinity to ion channels (Ca L-Type, Na Typ II and K(ATP)) have been evaluated in *in vitro* assays. No relevant potential for inhibition were identified. In line with the pharmacology of S1P modulators, siponimod activates an inward-rectifying G protein-coupled potassium channel (GIRK/IKACh) in atrial myocytes. Electrophysiological investigations on the arrhythmogenic potential or QT interval prolongation in the coronary arteria and isolated rabbit heart did not reveal any specific electrophysiological effects up to the highest concentration tested (10 µM). Direct effects on the pacemaker activity in isolated rabbit hearts showed minor effects on cycle length in 2/6 experiments. Coronary blood flow (by indirect measurement of the coronary perfusion rate) was not affected up to 10 µM. *In vivo,* transient decrease in heart rate was identified in all tested species (rat, rabbit, guinea pig and monkey). No adverse cardiovascular effects or clinically relevant ECG changes were observed in a single-dose GLP safety pharmacology study in monkey up to the maximum tolerated single dose of 150 mg/kg (Cmax: >50 µM). Increases in the QT interval (without correction factor) and a second-degree AV block were identified in 1 monkey in a non-GLP study at the highest dose tested of 100 mg/kg. In repeat dose toxicity studies in monkey, there were no adverse cardiovascular effects or clinically relevant ECG changes noted over an exposure duration of 2, 4, 26 and 52 weeks. Siponimod does not belong to a chemical/pharmacological class in which some members have been shown to induce QT interval prolongation in humans. Overall, cardiovascular effects were present in all nonclinical species tested and were characterized by transient bradyarrhythmia and effect on atrioventricular conduction, *via* activation of GIRK channel; importantly no relevant effects on QT interval were identified.

Clinical Cardiac Safety

- In the completed 20 Clinical Pharmacology studies, a total of 1281 study participants have been enrolled, of which approximately 880 healthy subjects, 24 hepatic impaired subjects and 8 renal impaired subjects have received siponimod (roughly 434 received placebo or sequentially placebo/siponimod) and 363 received other drugs alone or in combination with siponimod.
- Healthy subjects have received siponimod as single doses or as multiple doses (single doses: 0.1 mg to 75 mg, multiple doses: 0.25 mg to 20 mg for up to 38 days).

Summary table - Number of subjects at different drug exposure levels (dose) in the 20 Clinical Pharmacology Studies

Treatment	Single Dose	Multiple Dose	Total[a]
BAF312 0.1 mg	11		11
BAF312 0.25 mg	156		156
BAF312 0.3 mg	8	15	23
BAF312 0.5 mg	8	94	102
BAF312 1 mg	8	101	109
BAF312 2 mg		66	66
BAF312 2.5 mg	21	16	37
BAF312 4 mg	90	64	154
BAF312 5 mg	16		16
BAF312 10 mg	20	32	52
BAF312 17.5 mg	8		8
BAF312 20 mg		18	18
BAF312 25 mg	8		8
BAF312 75 mg	8		8
BAF312 0.5 mg preceded by up-titration		12	12
BAF312 2 mg preceded by up-titration		236	236
BAF312 10 mg preceded by up-titration		120	120
BAF312 in combination	40	175	215
Comparator alone	42	188	230
BAF312 0.25 mg i.v.	15		15
BAF312 1 mg i.v.	17		17
Placebo	41	393	434

	All BAF	380	544	912
	Any treatment	421	872	1281

[a] Table includes Hepatic (N=24) and Renal (N=8) patients as well along with healthy subjects. Some subjects received both single and multiple doses of siponimod and hence numbers in the single and multiple dose columns do not always add up to the total number.

- The thorough QT study investigating the effects of therapeutic (2 mg) and supratherapeutic (10 mg) doses of siponimod on cardiac repolarization, as assessed by the time-matched, baseline- and placebo-corrected QTcF (ΔΔQTcF), demonstrated no direct QT prolonging effect of siponimod. Siponimod is not associated with an arrhythmogenic potential related to QT prolongation.
- In the TQT study, categorical analysis revealed no treatment-emergent QTcF values above 480 ms and no QTcF increases from baseline of more than 60 ms on any of the on-treatment assessment days.
- The QTcF profile in the pooled categorical analyses of predefined QTcF events based on 12-lead ECG and Holter ECG assessments across single and multiple dose studies in healthy subjects, as described in SCP Table 5-3, was overall consistent with the categorical QTcF analyses in the dedicated thorough QT (Study A2118).
- No cases of sudden death, Torsade de pointes, ventricular flutter/ventricular fibrillation, or seizures were detected/reported throughout the Clinical Pharmacology program.
- Episodes of presyncope (N=15) or syncope (N=1) were reported in a total of 16 subjects across different dose levels in the Clinical Pharmacology program, which were considered to be associated with a vasovagal reaction after blood draw and not related to siponimod intake.
- Asymptomatic episodes of ventricular arrhythmia detected in the Holter ECG and online cardiac monitoring included single ventricular extrasystoles, ventricular couplets, bigeminy and trigeminy, which were observed with similar incidence under siponimod treatment compared to other treatments (placebo and other drugs alone or in combination with siponimod).
- An asymptomatic, self-limiting episode of non-sustained ventricular tachycardia of 8 beats (reported as an AE) in one subject receiving a siponimod i.v. infusion of 0.25 mg over 3 h (A2126). Other episodes of non-sustained ventricular tachycardia (not reported as AEs, but detected in Holter ECG recordings), were reported infrequently (N=20 subjects), were asymptomatic, and without evidence of higher incidence under siponimod compared to placebo treatment.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DHANANJAY D MARATHE
10/12/2018
Hongshan Li was the primary reviewer.

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10/12/2018

Memorandum

To: Jeffrey Kraft, OMPT/CDER/OTS/OCP
via Nahleen Lopez, CDER/OND/ODEI/DNP
Center for Drug Evaluation and Research (CDER)/Office of New Drugs/Office of Drug Evaluation I/Division of Neurology Products (DNP)

From: Eveline Arnold, Scientific Reviewer, CDRH/OIR/DCTD
Center for Devices and Radiological Health/Office of In Vitro Diagnostics and Radiological Health/Division of Chemistry and Toxicology Devices

Subject: Inter-Center Consult Request

Date: January 25, 2018

Background:

The Division of Neurological Products (DNP) in CDER requests a consult from DCTD/OIR in CDRH seeking input regarding the need for a potential companion diagnostic test for Mayzent (siponimod). This request is based on the sponsor's proposal to exclude subjects with the CYP2C9*3/*3 genotype. DNP indicates that the development of the companion diagnostic test through a Post-Marketing Commitment (PMC) may be discussed, and would like CDRH's input regarding the need for a companion diagnostic test.

Siponimod (Mayzent) is currently under review in CDER under NDA209884 (submission date, July 26, 2018, Next FDA Action Date: March 26, 2019).

Review Scope:

CDER provided the following background information to CDRH/DCTD, regarding the development siponimod (Mayzent) in ICCR2018-04168, in an email dated December 21, 2018:

> "The underlying issue would be an assessment of the need for a companion diagnostic. The sponsor proposes excluding subjects with the CYP2C9 *3/*3 genotype…The sponsor did not develop a diagnostic but in earlier CDRH discussions feel like they need one for their indication. We would likely be requesting via a PMC with approval and would like CDRH to weigh in on the need for a device…"

DCTD's understanding of the review scope is as follows:

1. OCP is requesting a review to see if there is a need for a companion diagnostic for CYP2C9 genotyping since the sponsor is excluding *3/*3 subjects.

CDER also provided the following documents from the NDA by email:

- Early phase study to assess the impact of CYP2C9 phenotype on PK [BAF312A2128]
- Physiologically-based pharmacokinetic(s) (PBPK) for effects of CYP2C9 genetics on PK [Summary of Clinical Pharmacology] (sections 3.3.1.2.3 In silico data and 3.3.1.2.4 CYP2C9 genotype-based DDI management)
- Pivotal efficacy study where CYP2C9 *3/*3 patients were excluded [CBAF312A2304]
- Sponsor's draft labeling for siponimod (Mayzent)

While drafting this consult, DCTD referred to BAF312A2128 and the PBPK studies presented in the Summary of Clinical Pharmacology to understand how the CYP2C9 *3/*3 genotype affects siponimod exposure. DCTD also referred to the exclusion criteria in section 9.3.2 of CBAF312A2304 and the draft drug labeling.

CDRH/OIR/DCTD Comments:

According to the drug sponsor:

> "Siponimod is a novel sphingosine-1-phosphate (S1P) receptor modulator that reduces peripheral lymphocyte counts in blood. The mechanism of action is similar to that of the S1P receptor modulator fingolimod, but siponimod has different receptor selectivity than fingolimod. Fingolimod acts as an agonist on 4 out of 5 S1P receptors (S1P1, S1P3, S1P4, and S1P5); whereas, siponimod is a S1P1/S1P5-selective agonist and in contrast to fingolimod, siponimod does not require a phosphorylation step in vivo."

In BAF312A2128, the drug sponsor conducted an open-label study to assess the pharmacokinetics, safety and tolerability of siponimod in healthy subjects with CYP2C9 extensive (EM) and poor metabolizer (PM) phenotype. Subjects in BAF312A2128 were genotyped by third party vendor (b) (4). The sponsor concluded that the CYP2C9*2/*3 and CYP2C9*3/*3 genotype resulted in 2 and 4-fold higher AUCinf and AUClast, respectively, compared to extensive metabolizers (CYP2C9*1/*1). However, there was only a minor increase of Cmax. Based on the PBPK information provided by CDER, as well as discussion with Dr. Kraft on January 14, 2019, DCTD's understanding is that the CYP2C9*3/*3 genotype leads to higher exposure to siponimod.

With respect to safety or adverse event information for siponimod, the drug sponsor concluded that siponimod was safe and generally well tolerated in Phase I clinical pharmacology trials (BAF312A2128). There is limited adverse event data for siponimod in subjects with a CYP2C9*3/*3 genotype presented in this study, because the study enrolled only six (6) subjects with the CYP2C9*3/*3 genotype.

The sponsor conducted the pivotal study (CBAF312A2304), excluding patients with homozygosity for CYP2C9*3 (tested at screening), or patients who refused to test for

CYP2C9*3 haplotype. Following discussion with Dr. Kraft, CDRH's understanding is that this exclusion was potentially based on increased exposure to siponimod in subjects homozygous for *3/*3, rather than specific adverse event data in BAF312A2128. Dr. Kraft further explained that the sponsor may have excluded *3/*3 patients based on the drug sponsor's prior experience with the related drug fingolimod (NDA 022527), where increased exposure is associated with greater risk of adverse events[1]. As such, CDRH's understanding is that no safety data was obtained for patients with the CYP2C9*3/*3 genotype in the pivotal trial (CBAF312A2304), because of their exclusion from the trial.

Based on discussion with Dr. Kraft, CDRH's understanding is that CDER intends to contraindicate against the use of siponimod in patients with a homozygous *3/*3 genotype due to the lack of safety data. That is, the intended use population for siponimod would be identified by the results of CYP2C9 genotyping (contraindicated for use in patients with CYP2C9*3/*3 genotype). At this time, CDRH's understanding is that CDER has concluded that identification of an intended use population that excludes patients with the CYP2C9*3/*3 genotype is essential for the safe and effective use of siponimod. Therefore, such a CYP2C9 genotyping assay, if used to identify patients in the population for whom the therapeutic product has been adequately studied, and found safe and effective, would be consistent with the definition of a companion diagnostic in vitro diagnostic (IVD) device. CDRH is happy to provide feedback as needed to CDER and/or the sponsor as the sponsor continues through their product development plan.

CDRH strongly recommends that the drug sponsor, and/or the IVD sponsor identified by the drug sponsor, interact with CDRH through CDRH's pre-submission process as part of their product development plan for siponimod. CDRH also strongly recommends that the drug sponsor review FDA's guidance document entitled "In Vitro Companion Diagnostic Devices, Guidance for Industry and Food and Drug Administration Staff" (referred to as the Companion Diagnostic Guidance below), available online here:

https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm262327.pdf

CDRH is happy to discuss regulatory pathways and the development of an in vitro diagnostic device (IVD) for CYP2C9 genotyping through CDRH's pre-submission program. Information regarding CDRH's pre-submission program is available online, here:

https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm311176.pdf.

CDRH also has the following general comments for CDER's consideration:

1. Based on discussion with CDER, CDRH's current understanding is that siponimod should not be used in patients with the CYP2C9*3/*3 genotype, because safety of

[1] Fingolimod drug label: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/022527s26lbl.pdf (Accessed January 17, 2019)

siponimod has not been adequately studied in these patients. Currently, all legally marketed in vitro diagnostic (IVD) devices for CYP2C9 genotyping are intended as an aid in the identification of patients at risk for increased warfarin sensitivity. The drug sponsor now proposes an intended use for the identification of patients in the population who should not receive siponimod (i.e. patients with the CYP2C9*3/*3 genotype), which would constitute a new intended use. As stated in FDA's Companion Diagnostic guidance referenced above, if an IVD device is already legally marketed and the IVD device manufacturer intends to market its device for a new use as an IVD companion diagnostic device for a novel therapeutic product, FDA would likely consider the new use of the IVD device with the novel therapeutic product as a new use for the device that would require an additional premarket submission. The sponsor will therefore need to validate an IVD device, or identify a device manufacturer (e.g. a manufacturer of a currently legally marketed CYP2C9 genotyping IVD device) to validate an IVD device for this intended use, and provide the validation data to the Agency to support the new intended use in a premarket submission.

2. CDER proposes that the validation of an IVD companion diagnostic could be requested through a post-marketing commitment. As recommended in the Companion Diagnostic Guidance, if determined to be essential to the safety and efficacy of a novel therapeutic product, a companion diagnostic should be developed and approved or cleared contemporaneously as the novel therapeutic product, so that it will be available for use when the therapeutic product is approved. This may be challenging at this stage of review for the current NDA. As such, we recommend that the drug sponsor, and/or IVD sponsor identified by the drug sponsor, interact with CDRH as soon as possible. CDRH is happy to provide guidance and feedback as needed to the drug sponsor, and/or the IVD sponsor identified by the drug sponsor, on potential regulatory pathways for this device.

3. The low frequency of the *3 allele may make development and validation of a device intended to detect the *3/*3 genotype for the purpose of determining eligibility for spinomod challenging because of the limited availability of samples with relevant genotypes (e.g., *3/*3). However, because the drug sponsor conducted genotyping as part of the inclusion/exclusion process for the pivotal trial, the drug sponsor may have enough patient specimens with relevant genotypes to address this challenge. Please note that CDRH would need additional information regarding the clinical risk of incorrect results to determine the amount of data and the resulting analytical performance that would be adequate to support this new intended use. CDRH would be happy to discuss with CDER the types of risks related to incorrect results (e.g., determining a *3/*3 patient is eligible due to an incorrect genotyping results) so CDRH can determine the type/extent of data that would be appropriate to support this new claim. CDRH's pre-submission guidance document may be helpful for the sponsor for preparing materials for discussion with

CDRH, and can be found here:
https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm311176.pdf

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