CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209884Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

NDA 209884
Review # 01

Drug Name/Dosage Form	Siponimod Tablets
Strength	0.25 mg, 2 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Novartis Pharmaceuticals Corporation
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original	28-JUN-2018	*Amendment*	01-NOV-2018
Amendment	18-SEP-2018	*Amendment*	06-NOV-2018
Amendment	26-SEP-2018	*Amendment*	26-NOV-2018

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER	OPQ OFFICE
Drug Substance	Rajan Pragani	Suong Tran	ONDP
Drug Product	Mariappan Chelliah	Wendy Wilson-Lee	
Environmental			
Labeling			
Process	Xueli Zhu	Nallaperumal Chidambaram	OPF
Facility	Xueli Zhu	Ruth Moore	
Biopharmaceutics	Zhuojun (Joan) Zhao	Ta-Chen Wu	ONDP
Regulatory Business Process Manager	Dahlia Walters		OPRO
Application Technical Lead	Wendy Wilson-Lee		ONDP

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

No Type II or IV DMFs referenced.

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	76122	BAF312 for treatment of multiple sclerosis

2. CONSULTS

None

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends **APPROVAL** of NDA 209884 for Siponimod Tablets, 0.25 and 2 mg.

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	***For the treatment of secondary progressive multiple sclerosis***
Duration of Treatment	***Chronic***
Maximum Daily Dose	***2 mg***
Alternative Methods of Administration	***None***

Novartis seeks approval of siponimod tablets for the treatment of secondary progressive multiple sclerosis (SPMS). SPMS is characterized by a decrease in frequency of relapses and a steady accumulation of disability. Patients with SPMS often have reduced motion, cognitive impairment, visual impairment, fatigue, pain, depressed, and severe sphincter control issues. FDA granted fast track designation (September 2012) and rolling review (January 2018) (b) (4)). Siponimod is not approved for marketing in any country. Two approved therapies include SPMS in their labels in some countries – mitoxantrone (US) and interferon beta-1b (EU). The issue of regulatory starting materials and designation of siponimod fumaric acid as a co-crystal was discussed as part of an FDA CMC-only Type C meeting (August 2017).

Blend uniformity and content uniformity of the drug product is important due to the relatively low drug load. Development of a robust dissolution method is also important due to the relative poor solubility of the drug substance. Confirmation of the integrity of the purported co-crystal throughout the drug product manufacturing, packaging, and shelf life is a key issue. The proposed assay limit i (b) (4)% with a proposed NMT (b) (4) (b) (4) limit. Different limits are proposed for specified degradants in the drug product at release and on stability. The proposed container closures are HPDE bottles and (b) (4) blisters. The drug product stability data package includes 12 moths of long-term and 6 months of accelerated for three batches of each strength packaged in both container closure systems. These batches were manufactured at a site different than the proposed commercial drug product manufacturing facility.

B. Quality Assessment Overview

The drug substance review covers both the drug substance siponimod an (b) (4) (b) (4) siponimod fumaric acid, which is a 2:1 co-crystal (reference is made to FDA's guidance Regulatory Classification of Pharmaceutical Co-Crystals for the

designation of drug substance [redacted]'). Characterization data for the drug substance siponimod fumaric acid was reviewed and it was confirmed that the drug substance exists as a 2:1 co-crystal and not a salt; the cocrystal was selected to [redacted]. The drug substance exhibits poor solubility in most solvents except acetic acid and is characterized as highly permeable and non-hygroscopic. Several polymorphic forms had been identified in screening studies, but only one form [redacted] results from the commercial manufacturing process and on stability; [redacted]. The labeled strength is correlated with siponimod (not siponimod fumaric acid) which is consistent with naming policies for co-crystals.

A [redacted] mutagenic impurity assessment was conducted. The drug substance was tested and found not mutagenic. The strategy to test fo [redacted] in the drug substance specification covers the major mutagenic impurity classes. The limits fo [redacted] were adequate. The acceptability of the drug substance limits for the specified impurities was consulted out to the nonclinical reviewer and found adequate. Additionally, the nonclinical reviewer was notified of the [redacted] limit in the drug substance specification and it was determined adequate. Confirmation that the fumaric acid provides no added clinical activity against Multiple Sclerosis was confirmed by the clinical review team.

Regarding stability, the Applicant was asked to provide three-month long-term and accelerated stability data for the three commercial-scale batches (B458004, B458005, B458006) of siponimod fumaric acid produced at the intended commercial manufacturing site o [redacted] The Applicant complied to demonstrate comparability of the new [redacted] site to the Novartis manufacturing site in Basel, Switzerland, which produced the registration batches. **Based on the stability data provided for the registration batches, a retest date of [redacted] (up to [redacted] °C) is acceptable for siponimod fumaric acid.**

The drug product is a film-coated, immediate-release tablet for oral administration manufactured in two strengths – 0.25 mg and 2 mg based on the siponimod active moiety. The formulation consists of common excipients although [redacted] was chosen as th [redacted] The proposed maintenance dose is 2 mg per day with the 0.25 mg strength intended for use during the titration phase only. Early development relied on a capsule formulation containing 2.5 mg, 25 mg, and 100 mg of siponimod. Phase II trials used 0.1 mg, 0.25 mg, 1 mg, 4 mg, and 5 mg tablets. Phase III studies used 0.25 mg, 0.5 mg, 1 mg, and 2 mg tablets that differ from the proposed commercial formulation only in th [redacted] The Phase III materials, registration stability, and confirmatory drug product batches used drug substance with particle size distributions that comply with the proposed commercial specification limit. The formulation contains compendial excipients. The maximum daily exposure for all the excipients based on the proposed maximum daily dose are within previous use levels of these excipients in approved oral dosage forms.

The proposed drug product specification is adequate to ensure the quality of the siponimod 0.25 mg and 2 mg tablets. While larger particle size is detrimental for the dissolution and content uniformity, the smallest particles affect the stability. Therefore, the Sponsor's choice of acceptance criterion (b) (4) (b) (4) is an acceptable choice. Additionally, the API batches used in the Phase-III, primary stability, and confirmatory batches of the drug product had the same criteria for the particle size as proposed for the commercial batches. Therefore, the proposed criteria for API particle size is acceptable. All non-compendial analytical procedures are validated and considered suitable as regulatory methods for their intended purposes. FDA Laboratories verified the dissolution by HPLC; uniformity of dosage units by content uniformity by HPLC; and identity, assay, and degradation products by HPLC analytical procedures. **While no major deficiencies were identified, several recommendations were included in the method verification report for inclusion in the action letter.** Three new degradants specific to the drug product were identified. These new degradants are adequately controlled and considered qualified at the proposed limits.

Standard HDPE bottles and (b) (4) closure were used in the registration stability batches and the same will be used for packaging the proposed commercial batches. The available stability data demonstrate that the primary container closure system provides adequate stability through the proposed shelf-life. Please note that the Applicant is also proposing to use comparable HDPE bottles and closures from a second supplier for the commercial packaging. But no stability data is provided for finished package corresponding to the second supplier. This is acceptable from a risk perspective.

The long-term stability data shows little change over time and little variability. The accelerated data shows some notable change over time. Given that the long-term data is amenable to statistical evaluation, per ICH Q1E, for drug products stored under refrigeration, a maximum of 6 months in shelf-life extrapolation may be granted. The Applicant's proposed shelf-life of 18 months for the HPDE bottles is in accordance with ICH Q1E. However, for the blisters, the Applicant is proposing only a shelf-life of 9 months, which is shorter than the available real time stability data. Because the statistical analysis predicts the assay for the 0.25 mg tablets in the blisters to decrease significantly faster than the same tablets packaged in the HDPE bottles, the Applicant has taken a conservative approach and set the shelf-life as 9 months for this configuration. In summary, the shelf-life may be granted as proposed by the Applicant:

- **A shelf life of 18 months may be granted for the 0.25 mg and 2 mg tablets packaged in HDPE bottles when stored at 2°C – 8°C (36°F – 46°F). The tablets may be stored at 20°C - 25°C (68°F to 77°F) for up to 1 month after dispensing.**
- **A shelf life of 9 months may be granted for the 0.25 mg tablets packaged in (b) (4) blisters (titration pack) when stored at 2°C – 8°C (36°F – 46°F). The tablets may be stored at 20°C - 25°C (68°F to 77°F) for up to 1 week after dispensing.**

The proposed manufacturing process for future commercial batches is the same as the clinical batches. The proposed manufacturing process has a minimum stress to the proposed drug substance. Drug substance particle size was identified as a potential critical attribute which impacts the drug product content uniformity. Therefore, this attribute was extensively studied at lab scale and specifications for drug substance particle size were put in place to ensure robust processing within the defined specifications. (b) (4)

(b) (4) Controls necessary for the manufacture and control of Siponimod (BAF312) 0.25 mg and 2 mg film-coated tablets are conducted in accordance with cGMP to prevent microbial contamination. With supporting data, the applicant demonstrated that the proposed Commercial batches can be adequately and consistently manufactured with all critical quality attributes the same as the clinical batches.

The Biopharmaceutics review is focused on the evaluation of the adequacy of the overall information/data supporting proposed dissolution method and acceptance criterion, as well as formulation bridging in product development. In Vitro Dissolution Method and Acceptance Criterion: Based on the provided dissolution data, the following dissolution methods and the revised acceptance criterion are acceptable and agreed upon:

- Apparatus: USP II (Paddle)
- Rotation Speed: 50 RPM
- Medium: 6.8 Phosphate Buffer with 0.1% (m/v) Polysorbate 80
- Volume: 900 mL (for 2 mg) and 500 mL (for 0.25 mg)
- Cumulative % of Drug Dissolved (Label Claim): NLT (b) (4)% (Q) at 20 minutes

The Applicant provided sufficient information to support the bridging the proposed commercial Siponimod Tablets, 0.25 mg and 2 mg, to the clinical formulation (or final market image (FMI)) Siponimod Tablets used in Phase 3 clinical trials, showing there is no impact of color change, debossing or drug product manufacture site.

All facilities were evaluated and deemed acceptable. The claim for categorical exclusion is acceptable in accordance with 21 CFR 25.31(b) and 25.15(d).

C. Special Product Quality Labeling Recommendations (NDA only)

C. Special Product Quality Labeling Recommendations (NDA only)

None

D. Final Risk Assessment

From Initial Risk Identification			Review Assessment		
Critical Quality Attribute	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay	Formulation Container Closure Process Parameters Scale/Equipment Site	**Low**		**Acceptable**	
Solid State	Formulation Raw Materials Container Closure Process Parameters Scale/Equipment Site	**Medium**	(b) (4)	**Acceptable**	
Content Uniformity	Formulation Raw Materials Process Parameters Scale/Equipment Site	**High**		**Acceptable**	

From Initial Risk Identification			Review Assessment		
Critical Quality Attribute	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Dissolution	Formulation Raw Materials Process Parameters Scale/Equipment Site	**Medium**	(b) (4)	**Acceptable**	
Microbial Limits	Formulation Raw Materials Process Parameters Scale/Equipment Site	**Low**		**Acceptable**	

Wendy
Wilson- Lee

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LABELING

I. Package Insert

1. *Highlights of Prescribing Information*

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	[PROPRIETARY NAME] ™ (siponimod)
Dosage form, route of administration	Tablets, for oral administration
Controlled drug substance symbol (if applicable)	N/A
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Tablets: 0.25 mg and 2 mg. Adequate

2. *Section 2 Dosage and Administration*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	N/A

3. *Section 3 Dosage Forms and Strengths*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	tablets
Strengths: in metric system	0.25 mg and 2 mg
Active moiety expression of strength with equivalence statement (if applicable)	Adequate. See next row.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	0.25 mg tablet: Pale red, unscored, round biconvex film-coated tablet with beveled edges, debossed with ⏻ on one side & 'T' on other side. 2 mg tablet: Pale yellow, unscored, round biconvex film-coated tablet with beveled edges, debossed with ⏻ on one side & 'II' on other side.

4. ***Section 11 Description***

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	[PROPRIETARY NAME] siponimod
Dosage form and route of administration	tablets
Active moiety expression of strength with equivalence statement (if applicable)	Each film coated tablet contains 0.25 mg or 2 mg siponimod, equivalent to 0.28 mg or 2.22 mg as 2:1 co-crystal of siponimod and fumaric acid, respectively.
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	N/A
Statement of being sterile (if applicable)	N/A
Pharmacological/ therapeutic class	Siponimod is a sphingosine 1-phosphate receptor modulator.
Chemical name, structural formula, molecular weight	Siponimod is present as 2:1 co-crystal of siponimod and fumaric acid and has the following chemical name: 1-[[4-[(1*E*)-1-[[[4-Cyclohexyl-3-(trifluoromethyl)phenyl]methoxy]imino]ethyl]-2-ethylphenyl]methyl]-3-azetidinecarboxylic acid (2*E*)-2-butenedioate (2:1). Its molecular formula is $C_4H_4O_4$. $2C_{29}H_{35}F_3N_2O_3$ and its molecular weight is 1149.29 g/mol.
If radioactive, statement of important nuclear characteristics.	N/A
Other important chemical or physical properties (such as pKa or pH)	It is a white to almost white powder.

5. ***Section 16 How Supplied/Storage and Handling***

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	0.25 mg and 2 mg
Available units (e.g., bottles of 100 tablets)	0.25 mg: blisters containing 12 tablets and bottles containing 28 tablets. 2 mg: bottle of 30 tablets
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	0.25 mg tablet (equivalent to 0.28 mg siponimod fumaric acid): Pale red, unscored, round biconvex film-coated tablet with beveled edges, debossed with  on one side and 'T' on other side. 2 mg tablet (equivalent to 2.22 mg siponimod fumaric acid): Pale yellow, unscored, round biconvex film-coated tablet with beveled edges, debossed with  on one side and 'II' on other side.
Special handling (e.g., protect from light)	N/A
Storage conditions	2°C– 8°C (36°F to 46°F). After dispensing, the blisters can be stored at controlled room temperature for up to 1 week and the bottles for up to 1 month.
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Adequate

Reviewer's Assessment of Package Insert: ***Adequate***

The proposed prescribing information meets the appropriate rules and regulations from the CMC perspective. However, it must be noted that the drug substance is considered a co-crystal of siponimod and fumaric acid. Based on the internal discussion with OPPQ and OLDP, it was determined that the established name "siponimod" will be used throughout the labeling (Please refer to the Memorandum of Meeting Minutes dated xx-Dec-2018.). However, module 11 of the prescribing information (PI) and container/carton labels should have strength equivalency expressions in terms of co-crystal of siponimod and fumaric. This reviewer has edited the PI accordingly. However, the PI may be subjected to additional edits.

II. Labels:

1. ***Container Labels***

The most recent versions of the carton and container labels reviewed here are from eCTD seq. 0003. As a representative example, the container label corresponding to the 2 mg tablets in HDPE bottles is shown below:

(b) (4)

2. ***Carton Label***

Only the blister packaging (12 x 0.25 mg tablets) has the carton container and a blister sleeve as the secondary packaging. The carton label is shown below:

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Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	MAYZENT (siponimod)	MAYZENT (siponimod)
Dosage strength	2 mg or 0.25 mg	0.25 mg
Net contents	Adequate	Adequate
"Rx only" displayed prominently on the main panel	Adequate	Adequate
NDC number (21 CFR 207.35(b)(3)(i))	Adequate	
Lot number and expiration date (21 CFR 201.17)	Adequate	
Storage conditions	2°C– 8°C (36°F to 46°F). After dispensing, the blisters can be stored at controlled room temperature for up to 1 week and the bottles for up to 1 month.	
Bar code (21CFR 201.25)	Adequate	
Name of manufacturer/distributor	Product of Switzerland Dist. by: Novartis, East Hanover, NJ 07936	
And others, if space is available	n/a	n/a

Reviewer's Assessment of Labels: ***Adequate***

The container/carton labeling meets the appropriate rules and regulations from the CMC perspective. As discussed above, the container/carton labels should have strength equivalency expressions in terms of co-crystal of siponimod and fumaric. We will be requesting the Applicant to make such edits.

List of Deficiencies: None

Overall Assessment and Recommendation: Adequate

Primary Labeling Reviewer: Mariappan Chelliah

Secondary Reviewer: Wendy Wilson-Lee

Mariappan Chelliah

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BIOPHARMACEUTICS

Product Background:

NDA/ANDA: 209884-ORIG-1 [505(b)(1)]

Drug Product Name / Strength: Siponimod (BAF312) tablets, 0.25 and 2 mg

Route of Administration: Oral

Proposed Indication: Treatment of Secondary Progressive Multiple Sclerosis (SPMS)

Applicant Name: Novartis Pharmaceuticals Corporation

Primary Reviewer: Joan Zhao, Ph.D.

Secondary Reviewer: Ta-Chen Wu, Ph.D.

Review Summary:

Siponimod (BAF312) tablet is proposed for the treatment of secondary progressive multiple sclerosis (SPMS). The drug product is a film-coated, immediate-release tablet for oral administration, manufactured in two strengths, 0.25 mg and 2 mg based on the siponimod active moiety (b) (4)

The Biopharmaceutics review is focused on the evaluation of the adequacy of the overall information/data supporting proposed dissolution method and acceptance criterion, as well as formulation bridging in product development.

In Vitro Dissolution Method and Acceptance Criterion:

Based on the provided dissolution data, the following dissolution methods and the revised acceptance criterion are acceptable and agreed upon:

Apparatus	Rotation Speed	Medium	Volume	Cumulative % of Drug Dissolved (Label Claim)
USP II (Paddle)	50 RPM	pH 6.8 phosphate buffer with 0.1% (m/v) polysorbate 80	900 mL (for 2 mg) 500 mL (for 0.25 mg)	NL (b) (4)% (Q) at 20 minutes

Formulation Bridging:

The Applicant provided sufficient information to support the bridging the proposed commercial Siponimod Tablets, 0.25 mg and 2 mg, to the clinical formulation (or final market image (FMI)) Siponimod Tablets used in Phase 3 clinical trials, showing there is no impact of color change, debossing or drug product manufacture site.

RECOMMENDATION:

Based on the review of the overall information, from a Biopharmaceutics perspective, NDA 209884 for Siponimod (BAF312) tablets, 0.25 and 2 mg, is recommended for **APPROVAL**.

BIOPHARMACEUTICS ASSESSMENT

List of Submissions being reviewed:

Submissions Reviewed	Document Date
Original Rolling Submissions (S0000 and S0003)	3/28/2018 and 6/28/2018
Information Response (S0024)	11/1/2018

I. Drug Substance

The drug substance ($C_4H_4O_4 \cdot 2C_{29}H_{35}F_3N_2O_3$), a co-crystal of siponimod and fumaric acid, is a white to almost white, non-hygroscopic crystalline powder.

(b) (4)

II. BCS Designation: N/A

The Applicant notes that the drug substance, Siponimod Fumaric Acid, behaves like a BCS Class 2 compound with low solubility (Table 1) and high permeability for the 0.25 and 2 mg dosage strengths. No official BCS designation request is submitted.

Drug Substance Solubility:

Siponimod Fumaric Acid contains two acidic functionalities with experimentally determined pK_a values of 8.6 and 3.3.

The low solubility of Siponimod Fumaric Acid over the physiologic pH range is presented in Table 1.

Table 1. Solubility of Siponimod Fumaric Acid at 37.0 ± 0.5 °C

Solvent	Solubility (mg/mL)
Water	<0.0006
Simulated gastric fluid	<0.0006
Simulated intestinal fluid	0.94
pH 2.0 (USP HCl buffer)	<0.0006
pH 4.5 (USP acetate buffer)	<0.0006
pH 6.8 (USP phosphate buffer)	0.09
pH 7.5 (USP phosphate buffer)	0.23
FaSSIF	0.67
FeSSIF	10.10

FaSSIF = Fasted State Simulated Intestinal and Stomach Fluids; FeSSIF = Fed State Simulated Intestinal and Stomach Fluids.

Permeability:

The Applicant performed in vitro permeability studies, DMPK R0800531 and DMPK R1300921, using Caco-2 cells. The Applicant reported that API is a highly permeable compound.

III. Formulation:

Table 2 summarizes the qualitative and quantitative compositions of the proposed Siponimod tablets, 0.25 and 2 mg. Both strengths were studied in Phase 3 clinical studies.

Table 2. Composition of the Proposed Siponimod tablets, 0.25 and 2 mg

Ingredients	Amount per 0.25 mg film-coated tablet (mg)	Amount per 2 mg film-coated tablet (mg)	Function	Reference to standards
Tablet core:				
Tablet core				
Siponimod fumaric acid[1]	0.2 (b) (4)	2.22 (b) (4)	Drug substance	Novartis monograph
Lactose monohydrate	(b) (4)		(b) (4)	Ph. Eur., USP/NF
(b) (4) Microcrystalline cellulose				Ph. Eur., USP/NF
Crospovidone				Ph. Eur., USP/NF
(b) (4) Glyceryl behenate				Ph. Eur., USP/NF
(b) (4) Colloidal silicon dioxide				Ph. Eur., USP/NF
Weight of tablet core:				
Film-coating				
(b) (4)				Novartis monograph
(b) (4) red[2]				Novartis monograph
yellow[2]				Novartis monograph
black[2]				Novartis monograph
(b) (4)	-	-		Ph. Eur., USP/NF
Total weight of film-coated tablet:	**89.60**	**89.60**		

[1] 1.11 (b) (4) of siponimod fumaric acid corresponds to 1 mg of siponimod.
[2] (b) (4) Coating composition is shown in Table 2-2.
(b) (4)

The proposed commercial Siponimod Tablets, 0.25 mg and 2 mg, differ from the clinical (or FMI) formulation used in Phase 3 studies (see ***Appendix I***) in coat color (changed from white to pale red (0.25 mg strength) and from white to pale yellow (2 mg strength)) and debossing.

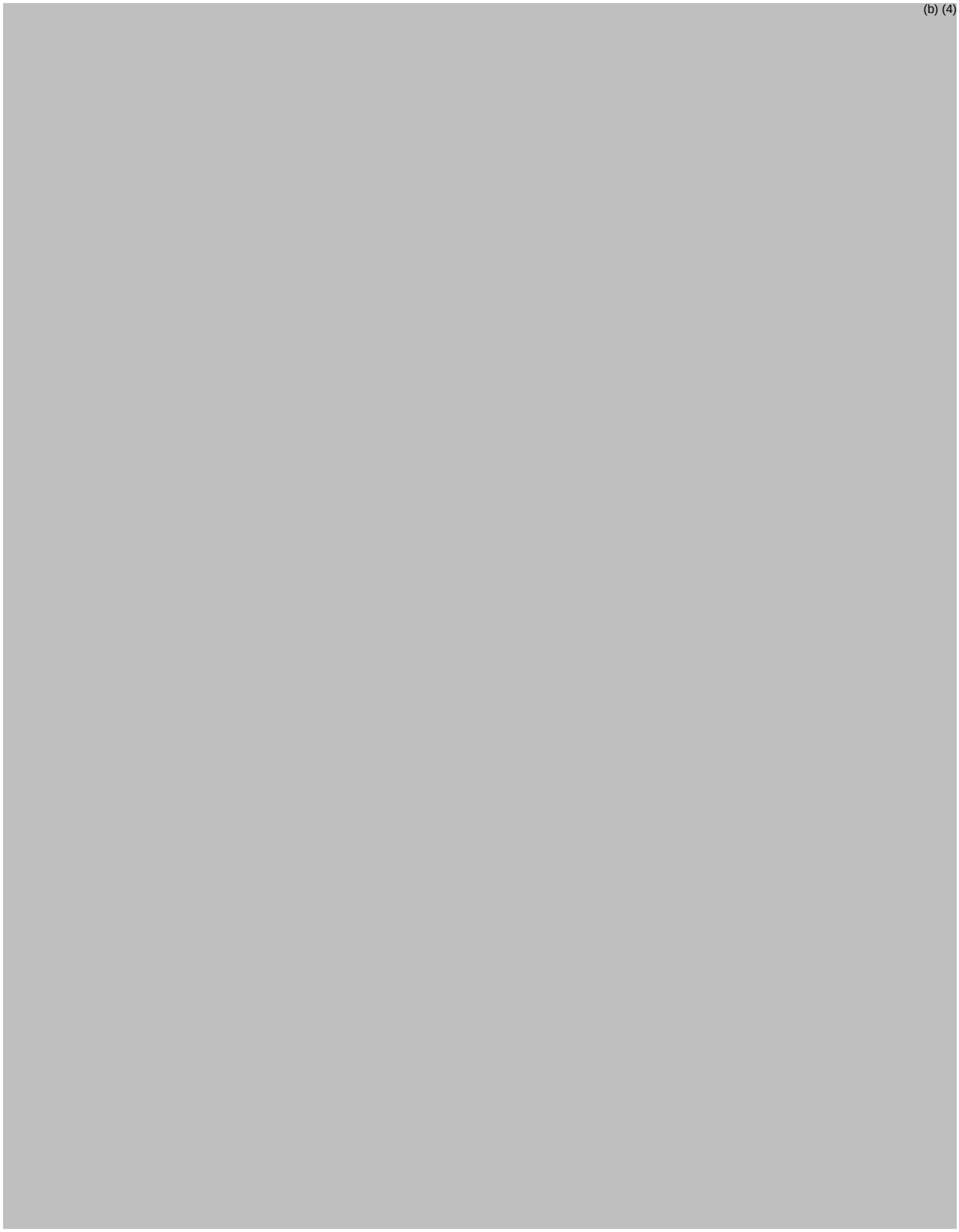
IV. Dissolution Method:

The proposed dissolution method is summarized as follows:

Strength	0.25 mg	2 mg
USP Apparatus type	USP II (Paddle)	
Rotation (rpm)	50 RPM	
Medium	pH 6.8 phosphate buffer with 0.1% (m/v) polysorbate 80	
Volume (mL)	500 mL	900 mL
Temperature	37±0.5 °C	

The Applicant provided the justification for the choice of dissolution apparatus, dissolution medium, and agitation speed as well as history of the dissolution method development (***Appendix II***) using the final market image (FMI) formulation in the Pharmaceutical Development Report in module 3.2.P.2, as detailed below:

(b) (4)



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Reviewer's Assessment of the dissolution method and method validation: Acceptable

Overall, the Applicant has demonstrated the suitability of the dissolution method for batch release and stability testing.

The dissolution method may have limited ability to detect variations in drug substance particle size or the amount of glyceryl behenate levels in the formulation, though it has not been properly investigated or demonstrated.

The proposed dissolution method (i.e. US Apparatus II (Paddle) at 50 rpm using 900 mL (for 2mg) and 500 mL (for 0.25 mg) pH 6.8 Phosphate buffer with 0.1% (m/v) Polysorbate 80) is found acceptable for the QC of the proposed drug product.

Dissolution Acceptance Criteria:

The Applicant proposed the dissolution acceptance criterion of Q (b)(4)% a (b)(4) minutes for both strengths using the proposed dissolution method.

Based on the dissolution data shown in Figures 8 and 9 (b)(4)% release i (b)(4) minutes), this Reviewer recommended a dissolution acceptance criterion of Q (b)(4)% (Q) a (b)(4) minutes for the proposed drug product. The recommended acceptance criterion was conveyed to the Applicant during the review cycle (see ***Appendix III***).

Figure 8. Dissolution profiles of BAF312 0.25 mg FMI tablet batches used in clinical (C) bioequivalence (X198 0811), registration stability (R) and confirmatory batch studies (CB), pH 6.8, 0.1 % Polysorbate 80, 50 rpm

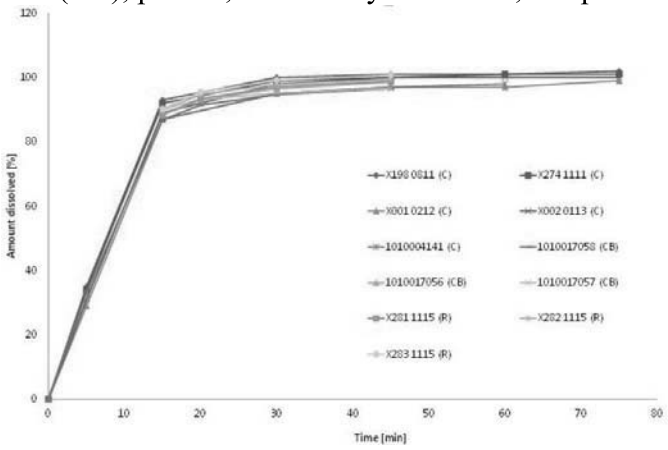
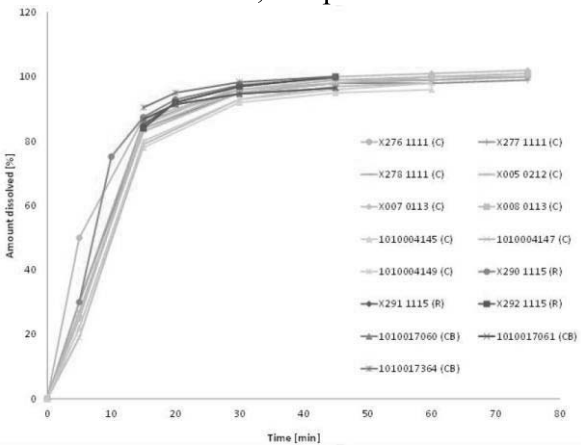


Figure 9. Dissolution profiles of BAF312 2 mg FMI tablet batches used in clinical (C), registration stability (R) and confirmatory batch studies (CB), pH 6.8, 0.1 % Polysorbate 80, 50 rpm



Based on the dissolution data (Table 6 and Table 7) and the justification provided in the Applicant's response dated November 1, 2018 (***Appendix III***), the Applicant's revised acceptance criterion of Q (b) (4)% at 20 minutes is found acceptable.

V. Bridging of Formulations:

The proposed commercial siponimod tablets, 0.25 mg and 2 mg (Table 2), differ from the FMI formulation (***Appendix I***) used in Phase 3 clinical studies in coat color (changed from white to pale red (0.25 mg strength) and from white to pale yellow (2 mg strength)). Iron oxides are introduced to the (b) (4) immediate release film coating of the proposed commercial siponimod tablets. In addition to the different coating colors, the two strengths of the proposed commercial siponimod tablets are distinguished by different debossing. The Applicant introduced the changes in the debossing after the manufacture of the registration stability batches.

The Applicant also transferred the drug product manufacture from the development sites (Novartis Basel an (b) (4) to the site of intended commercial manufacture site (Novartis Stein AG). Per process review[2] (b) (4)

The Applicant provided in vitro dissolution testing in (b) (4) (b) (4) comparing FMI and the proposed commercial formulation to assess the color and drug product manufacturing site changes.

[2] Panorama: Xueli Zhu_209844 IQA_Process Rev2.docx

Table 5. *f*2 similarity comparison for Siponimod (BAF312) 2 mg Film Coated Tablets pre-change vs. post-change (color and manufacturing site) demonstrating similarity.

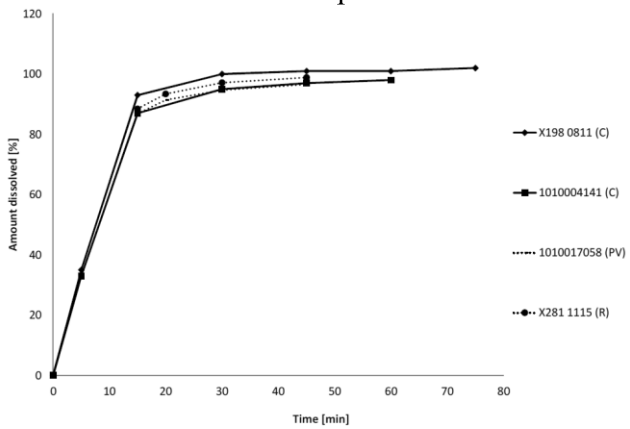
Strength (mg)	Batch type	(b) (4)	f_2 *similarity*
2*	Clinical vs. Registration stability		Similar
	Clinical vs. Commercial		Similar

Clinical = 1010004145 (used in Study CBAF312[3], manufactured by Novartis Basel),
Registration stability = X290 1115 (Manufactured by (b) (4)
Commercial = 1010017060 (New debossing, Manufactured by Novartis Stein AG)

The data in Table 5 show that the color change and the manufacturing site change (Basel, Rottendorf and Stein) from clinical batch to registration stability batch or to commercial batch of 2 mg did not impact the dissolution profile.

The Applicant also provided dissolution profiles of 0.25 mg clinical, registration stability, and commercial production batches using the QC method (Figure 10)[4].

Figure 10. Dissolution profiles of BAF312 0.25 mg of Clinical (C), commercial production, and registration stability batches pH 6.8 0.1% polysorbate 80 at paddle speed of 50 rpm



Commercial batch 1010017058 (PV, new debossing, manufactured by Novartis Stein AG)
Registration batch X281 1115 (R, Manufactured by (b) (4)
Clinical batch X198 0811 (used in BAF312A2111[3], manufactured by Novartis Basel)
Clinical batch 1010004141 (used in BAF3122201E1[3], manufactured by Novartis Basel).

Bridging was demonstrated for the proposed commercial Siponimod Tablets, 0.25 and 2 mg manufactured by Novartis Stein to the clinical batches manufactured by Novartis Basel.

VI. Biowaiver Request:

The proposed commercial Siponimod tablets have 2 dosage strengths, 0.25 mg and 2 mg. Both strengths were used in clinical trials and thus no biowaiver request in the submission.

[3] \\cdsesub1\evsprod\nda209884\0003\m3\32-body-data\32p-drug-prod\baf312-fct\32p2-pharm-dev\pharmaceutical-development-ctfo.pdf

[4] The reviewer also reviewed additional dissolution profiles of 0.25 mg strength and corresponding in vivo data provided in module 3.2.P.2 for information only.

R Regional Information

Comparability Protocols: N/A

Lifecycle Management Considerations: N/A

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