CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216956Orig1s000

OTHER REVIEW(S)

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 Memo for Pregnancy Safety Concerns

Date:	October 12, 2023
Reviewer:	Sally Peprah, PhD MSPH Division of Epidemiology I
Team Leader:	Benjamin J. Booth, PhD MS Division of Epidemiology I
Deputy Division Director:	Wei Hua, MD PhD MHS MS Division of Epidemiology I
Subject:	ARIA Sufficiency Memo
Drug Name:	Velsipity (Etrasimod)
Application Type/Number:	NDA 216956
Applicant/sponsor:	Arena Pharmaceuticals Inc., a wholly owned subsidiary of Pfizer Inc.
OSE RCM #:	2022-2364

1. BACKGROUND INFORMATION

1.1. Medical Product

On October 14, 2022, Pfizer, Inc. submitted a new drug application (NDA) for new molecular entity (NME) etrasimod (also referred to as APD334, APD334 L-arginine or AR401959). Etrasimod is an orally administered, bioavailable sphingosine 1-phosphate (S1P) receptor modulator with selective activity at S1P that partially and reversibly sequesters specific lymphocytes in lymph nodes. The proposed indication for the current application is for the treatment of (b) (4) moderate to severe ulcerative colitis (UC) at a recommended dose of 2 mg (oral tablet) once daily. At the time of this review, etrasimod had not been authorized for marketing in the United States.

1.2. Describe the Safety Concern

The Division of Gastroenterology (DG) requested that the Division of Epidemiology-I (DEPI) assess the sufficiency of ARIA for broad-based safety signal detection studies among women exposed to etrasimod during pregnancy.

Safety during pregnancy due to drug exposure is a concern for women who are pregnant or of childbearing potential. 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.[1] The risk of disease flare and poor pregnancy outcomes in patients with UC is greatest in those who have active disease at the time of conception.[2,3] Poor pregnancy outcomes include antepartum hemorrhage, preterm delivery, and low birth weight infants. The risk of congenital abnormalities does not appear to be increased in patients with UC.[4] However, the S1P receptor plays an important role in embryogenesis, including vascular and neural development.[5] Currently, there are four S1P receptor modulators approved by the FDA: fingolimod, siponimod, ozanimod and ponesimod with only ozanimod being approved for the treatment of UC. The other S1P receptor modulators listed above are approved for the treatment of multiple sclerosis (MS).

Throughout the etrasimod clinical development program, pregnant females were excluded from study participation. Females of reproductive potential were to use effective contraception methods during treatment and for at least 30 days after their last dose. Hormonal, barrier or abstinence contraception methods were permitted. Male subjects with a pregnant or non-pregnant female of childbearing potential partner were to use condoms during treatment and for 30 days following treatment. Females who became pregnant during an etrasimod study were required to discontinue study treatment.[6]

In the clinical development program, pregnancies were recorded in seven female subjects and one female partner of a male subject who received etrasimod. Outcomes of these pregnancies as of January 31, 2022, were as follows:

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[1] 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 March 17, 2021.
[2] Kratz K, Dinatale M, Yao PL. Division of Pediatric and Maternal Health Review of Etrasimod. U.S. Food and Drug Administration, Silver Spring (MD). Submitted to NDA 216956/S-023 (DARRTS Reference ID: 5169490) on May 05, 2023.
[3] Sun W, Dinatale M, Yao PL. Division of Pediatric and Maternal Health, Post-Marketing Requirement Memo for Zeposia (ozanimod). Submitted to NDA 209899 (DARRTS Reference ID: 4757744) on March 5, 2021.
[4] See footnote 2.
[5] See footnote 3
[6] Applicant's submitted background package, Module 2.5, Clinical Overview, page 87.

- 3 pregnancies were ongoing
- 2 pregnancies resulted in elective terminations
- 2 pregnancies resulted in spontaneous abortions in the first trimester
- 1 pregnancy was an ectopic pregnancy

After reviewing the submitted data, DPMH concluded that the eight pregnancies do not provide adequate information on the fetal or maternal risks associated with etrasimod exposure during pregnancy.[7] Additionally, DPMH concluded that the nonclinical data suggest fetal risks of demise or malformations (neural, cardiac, and/or skeletal) with exposure to etrasimod in utero. Thus, based on animal studies and the mechanism of action for this S1P receptor modulator and all others that have been approved, DPMH recommends that DG include text in the labeling about the possibility of fetal harm in section 5 under "Embryofetal Toxicity," and in subsection 8.1 under "Risk Summary" and "Animal Data".[8]

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

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 childbearing 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.***

[7] See footnote 3.
[8] Ibid.

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 such as a case-control study design will be considered if there is a need to collect additional information from the mothers through personal interviews, to obtain additional information on infants, to request permission to review medical records, or to perform long-term follow-up of their offspring, and such a study maybe nested within an electronic database study or conducted independent of it.

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:

Covariates: A descriptive pregnancy registry study requires the collection of detailed and specific information about important potential covariates such as family history of the disease or outcomes, lifestyle factors such as prenatal supplements, body mass index and illicit drug use. However, ARIA does not have detailed information on potential confounders for the pregnancy registry.

Outcomes: The pregnancy registry being considered requires that an expert clinical gynecologist or dysmorphologist review and classify medical records of all major congenital malformations; however, ARIA lacks access to medical records. Further, the prospective registry requires clinical information from medical records and risk factors that may not be available in claims data. Also, although in a first stage, the study using claims or electronic medical data may be algorithm-based, if it shows an imbalance in any of the outcomes being investigated, FDA may consider requiring outcome validation in the selected database(s) or a chart-confirmed analysis.

Analytical tools: ARIA data mining methods have not been fully tested and implemented in post-marketing surveillance of maternal, fetal, and infant outcomes.

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

Because etrasimod will be administered to females of reproductive potential and the risks of exposure to etrasimod during pregnancy are unclear the following PMRs are being proposed:

1) Conduct a prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to etrasimod-containing products regardless of indication during pregnancy to an unexposed control population. The registry should be designed to detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age births, preterm births, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, neonatal deaths, and infections, will be assessed through at least the first year of life.

2) Conduct an additional pregnancy study that uses a different design from the prospective pregnancy registry established to fulfill postmarketing requirement 2 (for example a retrospective cohort study using claims or electronic medical record data with outcome validation or a case-control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm births in women exposed to etrasimod-containing products regardless of indication during pregnancy compared to an unexposed control population.

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/s/

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WEI HUA
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JUDITH W ZANDER
10/12/2023 02:09:20 PM

SARAH K DUTCHER
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ROBERT BALL
10/12/2023 02:38:22 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	July 13, 2023
Requesting Office or Division:	Division of Gastroenterology (DG)
Application Type and Number:	NDA 216956
Product Name, Dosage Form, and Strength:	Velsipity (etrasimod) tablets, 2 mg
Applicant/Sponsor Name:	Pfizer, Inc. (Pfizer)
TTT ID #:	2022-2368-1
DMEPA 1 Safety Evaluator:	Sherly Abraham, R.Ph.
DMEPA 1 Team Leader:	Idalia Rychlik, Pharm.D.

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on June 27, 2023 for Velsipity. The Division of Gastroenterology (DG) requested that we review the revised container labels and carton labeling for Velsipity (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 Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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

[a] Abraham, A. Label and Labeling Review for Velsipity (NDA 216956). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 MAY 24. TTT ID No.: 2022-2368.

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/s/

SHERLY ABRAHAM
07/14/2023 09:24:36 AM

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07/14/2023 05:49:09 PM

Clinical Inspection Summary

Date	07/07/2023
From	Glenn Mannheim, M.D., Physician Min Lu, M.D., M.P.H., Lead Physician Jenn Sellers, M.D., Ph.D., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Anum Shami, PharmD, Regulatory Project Manager, DG Jamie Wolfe, M.D., Clinical Reviewer, DG Matthew Kowalik, M.D., Lead Physician, DG Jessica Lee, M.D., Division Director, DG Juli Tomaino, M.D., Deputy Director, DG
NDA #	216956
Applicant	Pfizer
Drug	Etrasimod (APD334; Velsipity, proposed proprietary name)
NME	Yes
Proposed Indication	Moderate-severe active ulcerative colitis (UC)
Review Priority	Standard
Consultation Request Date	11/30/2022
Summary Goal Date	7/13/2023
Action Goal Date	10/13/2023
PDUFA Date	10/14/2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three clinical investigators (Drs. Rafal Drozda, George DuVall and Timothy Ritter) and the Applicant, Pfizer, were inspected for Studies APD334-301 and APD334-302.

Based on inspection results, the clinical data generated by these sites for the above studies and submitted by the Applicant appear acceptable in support of this NDA.

II. BACKGROUND

This NDA is for the use of etrasimod (APD334) for the treatment of moderate to severe active ulcerative colitis (UC) [redacted] (b) (4) Efficacy and safety of etrasimod were assessed in two Phase 3 studies (APD334-301 and APD334-302).

APD334-301

This was a multicenter, randomized, double-blind, placebo-controlled, 52-week study to assess the efficacy and safety of etrasimod 2 mg tablets, administered orally once daily, in subjects with moderately to severely active UC. The subject population was to include 50% of each of the following categories: 1) those having had an inadequate response to: conventional therapy and are naïve to biologic or JAK inhibitor therapy; 2) those having had an inadequate response to, loss of response to, or intolerance to a biologic or JAK inhibitor (but, may have received

prior conventional therapy). The study consisted of a 28-Day Screening Period, a 12-Week Treatment Period, a 40-Week Treatment Period, and a 2-Week and 4-Week Follow-Up Period.

The primary objective was to assess the efficacy and safety of etrasimod on clinical remission in subjects with moderate to severe, active UC, after 12 and 52 weeks of treatment. The primary efficacy endpoints were the proportion of subjects achieving clinical remission at Weeks 12 and 52.

The study enrolled and randomized 433 subjects in 2:1 fashion to etrasimod 2 mg/day or placebo (etrasimod: 289; placebo: 144), of which, 207 subjects (etrasimod: 161; placebo: 46) completed the study; and 226 subjects (etrasimod: 128; placebo: 98) discontinued the study. Study subjects were from 37 countries.

The study was initiated on June 13, 2019 and was completed on February 16, 2022.

APD334-302

This was a multicenter, randomized, double-blind, placebo-controlled, 12-week study to assess the efficacy and safety of etrasimod 2 mg tablets, administered orally once daily, in subjects with moderate to severe, active UC. Randomization was 2:1 to etrasimod 2 mg/day or placebo.

The primary objective was to assess the efficacy and safety of etrasimod when administered for 12 weeks on clinical remission in subjects with moderately to severely active UC. The primary efficacy endpoint was the proportion of subjects achieving clinical remission at Week 12.

The study enrolled and randomized 354 subjects (etrasimod: 238; placebo: 116), of which, 316 subjects (etrasimod: 213; placebo: 103) completed the study; and 38 subjects (etrasimod: 25; placebo: 13) discontinued the study. Study subjects were from 39 countries containing 93 study sites.

The study was initiated on September 15, 2020 and was completed on December 07, 2021.

III. RESULTS (By Site):

1. George Aaron DuVall, M.D. /Site # 10004
1720 South Beckham Avenue
Tyler, TX 75701
Inspection Dates: 01/11-01/20/2023

A previous inspection of this site was conducted on 12/09/2021.

At this site, Studies APD334-301 and APD334-302 were reviewed during the inspection.

Study APD334-301: The site enrolled 12 subjects and 7 subjects completed the study.
Study APD334-302: The site enrolled 4 subjects with all 4 subjects completing the study. The first subject consented at this site on 01/28/2021 with the last consent occurring on 07/06/2021. The first subject randomization occurred on 03/02/2021 with the last on 06/03/2021. The last subject contact occurred on 08/27/2021.

Colonoscopy events for protocols APD334-302 and APD334-301 were conducted at Christus Trinity Mother Frances. The central reader for protocols APD334-302 and APD334-301 was Bioclinica and data was uploaded via online portal. Pulmonary function tests for protocols APD334-302 and APD334-301 were conducted at UT Health East Texas Physicians. Electrocardiograms were performed on-site for both protocols.

Records reviewed at this site included informed consent forms (ICFs), protocols, Institutional Review Board (IRB) correspondence, study approvals, sponsor and monitor correspondence, source records, test article accountability records, training records, Form FDA 1572, financial disclosures, and other regulatory documentation.

All enrolled subject records were reviewed for: informed consent; eligibility; primary efficacy endpoint (Protocol APD334-302 for Clinical remission at Week 12; Protocol APD334-301 for Clinical remission at Week 12 and Week 52); adverse events; protocol deviations; discontinuations; subject randomizations; and concomitant medications. No discrepancies were observed during the inspection.

The inspection found that the primary efficacy endpoint data was verifiable. There were no under reporting of AEs, SAEs; and deviations were reported according to the protocol.

In general, the inspection verified adequate source data and no significant deficiencies were identified.

2. **Timothy E. Ritter, MD /Site # 10074**
2485 E Southlake Blvd., Ste 100
Southlake, TX 76092-6687
Inspection Dates: 03/28-03/30/2023

A previous inspection of this investigator was conducted on 05/23/2019 with one discussion item related to an enrolled subject who did not have documentation to negate an exclusion criterion.

At this site, Study APD334-301 was reviewed during the inspection. A total of 11 subjects were screened from which 6 subjects enrolled. Of these, 2 subjects completed the study. The following records were reviewed during the inspection: informed consent forms (ICF),

protocols, institutional review board (IRB) correspondence and study approvals, sponsor and monitor correspondence, source records, test article accountability records, training records, Form FDA 1572, financial disclosures, and other regulatory documentation.

All enrolled subject records were reviewed for the following: informed consent; eligibility; primary efficacy endpoint (clinical remission); adverse events; protocol deviations; discontinuations; subject randomizations; and concomitant medications.

There was no underreporting of adverse events or deviations. All data reviewed matched with those provided in the data listings with the assignment.

The inspection found that the primary efficacy endpoint data was verifiable.

There was a single discussion item related to a clinical investigator not using the current ICF for two subjects.

In general, the inspection verified adequate source data and no significant deficiencies were identified.

3. **Rafal Drozda, MD/Site # 43034**
ul. Gen. Lucjana
Zeligowskiego 46/10
Lodz, Lodzkie 90-644
Poland
Inspection Dates: 03/13-03/15/2023

This is the first inspection of Dr. Drozda.

At this site, Study APD334-302 was reviewed during the inspection.

A total of 19 subjects were screened, of which 11 were screen failures, and the other 8 subjects were enrolled and randomized. No subjects discontinued from the study.

Records reviewed included: informed consent forms (ICF), protocols, Ethics Committee Documents with approval of the President of the Medicines Registration Office for the region of Lodz; financial disclosure forms; drug accountability; and records custody and retention.

The 8 study subject records were reviewed for discrepancies, of which, none were identified. The primary efficacy endpoint data was reviewed and found to be consistent with the data sets submitted for this study. There was no underreporting of AEs.

In general, the inspection verified adequate source data and no significant deficiencies were identified.

4. **Pfizer, Inc.**
10770 Science Center Drive
San Diego, CA 92121-3223
Inspection Dates: 05/01-05/05/2023

The study sponsor for APD334-301 and APD334-302 was Arena Pharmaceuticals, Inc. A previous inspection of Arena Pharmaceuticals, Inc occurred in 2010.

Arena Pharmaceuticals, Inc was founded in April 1997, and acquired by Pfizer in March 2022. The former Arena Pharmaceuticals location in San Diego was decommissioned and this inspection was conducted at Pfizer's facility in San Diego, California. Pfizer maintains the documentation for the clinical trials reviewed during this inspection.

A Clinical Study Team Lead, previously employed by Arena Pharmaceuticals since 2018, was present during the investigation to provide specific study information for Studies APD334-301 and APD334-302.

Study protocol APD334-301 was registered on ClinicalTrials.gov on May 10, 2019 and last updated with the results on 12/20/2022 under NCT03945188. The first subject was screened 5/15/2019 and the last subject visit date was 2/16/2022.

Study protocol APD334-302 was registered on ClinicalTrials.gov on June 24, 2019, and last updated with the results on 12/21/2022 under NCT03996369. The first subject was screened 8/18/2019 and the last subject visit date was 12/7/2021.

Clinical trial related information reviewed related to investigator agreements/Form FDA 1572s, investigator selection/training, financial disclosure, monitoring including selection and training, protocol compliance, IRB approval at sites, adverse events and serious adverse events including reporting, drug accountability, electronic systems used, and transfer of regulatory obligations and oversight of the two CROs (IQVIA and PSI) used.

Appropriate steps were taken by the sponsor/monitor/CRO to bring noncompliant sites into compliance. One clinical site (Site 10023) was terminated from the APD334-301 trial due to GCP non-compliance. Documentation related to the termination was reviewed during the inspection and it was confirmed there were no active subjects when the site was terminated.

The inspection reviewed the files from ten specific sites and conducted a trial wide review of any worldwide protocol deviations and no specific deviations were identified. There was no evidence of any under-reporting of serious adverse events.

In general, the sponsor's oversight and monitoring for the two studies appear adequate and no significant deficiencies were identified.

{See appended electronic signature page}

Glenn Mannheim, MD
Physician
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Min Lu, M.D.,
Lead Physician
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Jenn Sellers, M.D., Ph.D.
Branch Chief
Good Clinical Practice Assessment Branch
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cc:

Central Document Room/NDA 216956
Division of Gastroenterology /Division Director/Jessica Lee
Division of Gastroenterology/Deputy Director/Juli Tomaino
Division of Gastroenterology/Lead Physician/Matthew Kowalik
Division of Gastroenterology/Physician/Jamie Wolfe
Division of Gastroenterology/Regulatory Project Manager/Anum Shami
OSI/Office Director/David Burrow
OSI/Office Deputy Director/Laurie Muldowney

OSI/DCCE/Division Director/Kassa Ayalew
OSI/DCCE/GCPAB/Branch Chief/Jenn Sellers
OSI/DCCE/GCPAB/Team Leader/Min Lu
OSI/DCCE/GCPAB/Physician/Glenn Mannheim
OSI/GCPAB Program Analyst/Yolanda Patague
OSI/GCPAB Program Analyst/Loreto-Corazon Lim

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/s/

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JENN W SELLERS
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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 26, 2023

TO: Jessica Lee, M.D.
Director
Division of Gastroenterology
Office of New Drugs

FROM: Melkamu Getie Kebtie, Ph.D., R.Ph.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
DGDSI
OSIS

SUBJECT: Routine inspection of ICON Early Phase Services, LLC, San Antonio, TX

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of study APD334-114 (NDA 216956, etrasimod) conducted at ICON Early Phase Services, LLC, San Antonio, TX.

No objectionable conditions were observed, and Form FDA 483 was not issued at the inspection close-out. There were also no discussion items. Data from the audited study are reliable.

2. Inspected Study

NDA 216956

Study Number: APD334-114
Study Title: "A Phase 1, Open-Label, Randomized, Single-Dose, 3-Treatment, 3-Period Crossover Study in Healthy Subjects to Evaluate the Bioequivalence of Etrasimod 2 mg Proposed Commercial and Clinical Formulations, and to Assess the Effect of Food on the Pharmacokinetics of the Proposed Commercial Formulation"

Dates of conduct: 2/8/2021 (first subject enrolled) – 3/14/2021 (last subject last visit)

Clinical site: ICON Early Phase Services, LLC
8307 Gault Lane
San Antonio, TX
Clinical Investigator: Cassandra Key, MD

The APD334-114 trial was conducted under IND 125154.

3. Inspectional Findings

ORA investigator Joanne M Schlossin inspected ICON Early Phase Services, LLC, San Antonio, TX, from April 17-20, 2023.

The previous inspection for the clinical investigator Cassandra Key, was conducted in September 2022, and no Form FDA 483 was issued, but five items were discussed at the completion of that inspection. The discussion items included subjects not consenting to the current version of the ICF, insufficient documentation, and discrepancies between the source records and the eCRF and data listing. The current inspection did not observe similar findings.

The current inspection included auditing the following items:

- Case report forms (CRFs)
- Informed consent
- Inclusion/exclusion
- Subject enrollment
- Protocol deviations
- Test article accountability and storage
- Reserve samples
- Randomization
- Adverse events

At the conclusion of the inspection, investigator Schlossin did not observe any objectionable conditions and did not issue Form FDA 483. There were also no discussion items.

Melkamu Getie-Kebtie, Ph.D., R.Ph.
Pharmacologist

cc:
OTS/OSIS/Kassim/Mitchell/Fenty-Stewart/Haidar/Mirza
OTS/OSIS/DNDSI/Bonapace/Dasgupta/Ayala/Biswas
OTS/OSIS/DGDSI/Cho/Benson/Skelly/Au/Ou/Getie-Kebtie

ORA/OMPTO/OBIMO/ORA BIMO Inspection POC@fda.hhs.gov

Draft: MG 6/14/23, 6/21/23, 6/22/23, 6/23/23
Edit: SA 06/14/2023, 6/21/23, 6/22/23, 6/23/23; JC 6/23/23

OSIS File #: BE 9775

eNSpect Assignment ID: 217187
eNSpect OpID: 245231

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Team Lead

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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: June 23, 2023

To: Anum Shami, Project Manager, DG

From: Meeta Patel, Pharm.D., Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Adewale Adeleye, Pharm.D., Team Leader, OPDP

Subject: OPDP Labeling Comments for Velsipity (etrasimod) tablets, for oral use

NDA: 216956

In response to DG's consult request dated October 19, 2022, OPDP has reviewed the proposed product labeling (PI), Medication Guide (MG), and carton/container labeling for Velsipity.

OPDP has no comments on the PI or carton/container labeling.

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

Thank you for your consult. If you have any questions, please Meeta Patel at (301) 796-4284 or meeta.patel@fda.hhs.gov.

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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:	June 22, 2023
To:	Anum Shami Regulatory Project Manager **Division of Gastroenterology (DG)**
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:	Maria Nguyen, MSHS, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Meeta Patel, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	VELSIPITY (etrasimod)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 216956
Applicant:	Pfizer, Inc.

1 INTRODUCTION

On October 14, 2022, Pfizer, Inc., submitted for the Agency's review New Drug Application (NDA)/New Molecular Entity (NME) #216956 for VELSIPITY (etrasimod) tablets. The proposed indication for VELSIPITY (etrasimod) is for the treatment of moderately to severely active ulcerative colitis.

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 Gastroenterology (DG), on October 18, 2022, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for VELSIPITY (etrasimod) tablets, for oral use.

2 MATERIAL REVIEWED

- VELSIPITY (etrasimod) MG received on October 14, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 21, 2023.
- Draft VELSIPITY (etrasimod) Prescribing Information (PI) received on October 14, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 21, 2023.
- Approved ZEPOSIA comparator labeling dated September 29, 2022.
- Approved GILENYA comparator labeling dated December 26, 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)

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.

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

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/s/

MARIA T NGUYEN
06/22/2023 01:17:29 PM
DMPP-OPDP review of estrasimod (VELSIPITY) NDA/NME 216956 MG

MEETA N PATEL
06/22/2023 01:29:30 PM

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LASHAWN M GRIFFITHS
06/22/2023 01:52:13 PM

DIVISION OF PULMOLOGY, ALLERGY, AND CRITICAL CARE MEDICAL OFFICER CONSULTATION

Date:	June 7, 2023
To:	Division of Gastroenterology
From:	Rekha Jhamnani, Medical Officer, DPACC
Through:	Miya Paterniti, Medical Team Leader, DPACC
Through:	Banu Karimi-Shah, Acting Deputy Director, DPACC
Subject:	Etrasimod Pulmonary Safety and Labeling

General Information

NDA#:	216956
Applicant:	Arena Pharmaceuticals Inc.
Drug Product:	Etrasimod (APD334; Velsipity)
Request From:	Division of Gastroenterology
Date of Request:	October 14, 2022
Date Received:	October 19, 2022
Requested completion date:	May 25, 2023
Materials Reviewed:	NDA 216956 APD334-301 Clinical Study Report APD334-302 Clinical Study Report Proposed Label Response to Information Request February 8, 2023 Response to Information Request March 6, 2023 Response to Information Request March 9, 2023 Response to Information Request March 15, 2023 Response to Information Request March 21, 2023 Response to Information Request April 27, 2023 Response to Information Request May 31, 2023 NDA 22527 Fingolimod Label NDA 209884 Siponimod Label NDA 209899 Ozanimod Label NDA 213498 Ponesimod Label

I. Introduction

This is a Medical Officer response to the consultation request from the Division of Gastroenterology (DG), to review pulmonary function results for NDA 216956 for etrasimod, an oral sphingosine-1-phosphate (S1P) receptor modulator proposed for the treatment of (b) (4) moderately to severely active ulcerative colitis. DG also requested for the Division of Pulmonary, Allergy, and Critical Care (DPACC) to specifically comment on whether the proposed pulmonary safety labeling is acceptable.

The Applicant conducted two pivotal efficacy and safety studies (APD334-01 and APD334-02) that informed etrasimod's label and is the primary source of pulmonary function data. An overview of studies APD334-301 (ELEVATE UC 52) and APD334-302 (ELEVATE UC 12) is provided below, followed by DPACC's recommendations regarding pulmonary safety labeling.

II. Background

Etrasimod (APD334) is a new oral sphingosine-1-phosphate (S1P) receptor modulator, which is selective for $S1P_{1,4,5}$. 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 gastrointestinal tract. The target indication for etrasimod is moderately to severely active ulcerative colitis.

Pulmonary disease has been documented in inflammatory bowel disease (IBD) patients. Bronchiectasis is the most reported form of respiratory disease found in IBD patients. Bronchiolitis is the most reported small airway disease. Asthma also occurs with increased frequency in the IBD population. Venous thromboembolic disease also occurs with increased frequency in the IBD population. Many of the drugs used to treat IBD may also serve as a confounder for respiratory disease as they have respiratory side effects[1].

Several other S1P receptor modulators have been approved and will be briefly described below (in order of approval), with a focus on the pulmonary history. All drugs in this class are orally administered.

Fingolimod

Fingolimod (NDA 22527; Gilenya), another oral S1P receptor modulator, selective for $S1P_{1,5,}$ was the first S1P receptor modulator approved in September 2010 for relapsing-remitting multiple sclerosis. DPACC was consulted (see consult April 8, 2010) for fingolimod-related changes in pulmonary function. Based on safety findings, DPACC recommended labeling for drug-associated decline in pulmonary lung function. The current fingolimod label (revised 12/2019) 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

[1] Ji, Xiao-Qing et al. Pulmonary Manifestations of Inflammatory Bowel Disease. World J Gastroenterol Oct 2014: 13501-13511

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. DPACC 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. DPACC was consulted again (see consult November 22, 2021) to review the PMR pulmonary sub-study data. The data from this study were difficult to interpret due to small sample size after Month 24 as the study terminated early due to recruitment difficulties. It was also noted that it was challenging to interpret reversibility of pulmonary effects as it is difficult for MS patients to discontinue study drug as it may worsen their underlying MS. Thus, no labeling changes were recommended based on the PMR studies conducted by the Applicant.

Siponimod

Siponimod (NDA 209884; Mayzent), an $S1P_{1,5}$ receptor modulator, was approved in March 2019 for relapsing forms of multiple sclerosis. DPACC was consulted (see consult dated January 17, 2019) for siponimod-related changes in pulmonary function. DPACC recommended that siponimod include verbiage in Section 5 of the label to reflect observed changes in FEV1. The current label states under Section 5.4:

"Dose-dependent reductions in absolute forced expiratory volume over 1 second (FEV1) were observed in MAYZENT-treated patients 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% confidence interval (CI): 139, 37] at 2 years. The mean difference between MAYZENT-treated patients and patients receiving 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 Study 1, five 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."

Although the decline in FEV1 is similar to fingolimod, reversibility was not clearly established. Thus, a PMR was issued at the time of approval of siponimod: a prospective,

parallel cohort study in patients with relapsing forms of multiple sclerosis to assess the potentially serious risk of pulmonary toxicity. In November 2021, after fingolimod's PMR final study report was submitted, DPACC provided consult to the Division of Neurology on the request for release of PMR for siponimod. As noted above, the fingolimod PMR demonstrated difficulty in recruiting and retaining subjects in the PFT sub-study. Assessing reversibility was difficult as discontinuing S1P modulators can cause worsening of underlying MS symptoms. Because the pulmonary function changes and pulmonary adverse events were similar to fingolimod, DPACC agreed to release the Applicant from siponimod's PMR requirement. It was noted that the PFT data from the siponimod EXPAND clinical study cohort (long-term extension of the phase 3 study A2304) could be followed up in 2025 to obtain further information regarding pulmonary safety.

Ozanimod

Ozanimod (NDA 209899; Zeposia), an $S1P_{1,5}$ receptor modulator, was approved in 2020 for relapsing forms of MS and then in 2021 was the first S1P receptor modulator approved for moderately to severely active ulcerative colitis. DPACC was consulted for ozanimod-related changes in pulmonary function (see consults dated November 22, 2019 and January 28, 2021). A pooled analysis of pulmonary safety demonstrated dose-dependent changes in change from baseline in FEV1 and FVC as early as month 3, and the changes in FEV1 were sustained through month 12, while changes in FVC were not statistically significant at other timepoints. There were also statistically significant changes in change from baseline in percent predicted FEV1 and FVC. Analysis of PFT data after Month 12 was limited by decreases in sample size after Month 12.

The current label states under Section 5.7:

Dose-dependent reductions in absolute forced expiratory volume over 1 second (FEV1) were observed in MS patients treated with ZEPOSIA as early as 3 months after treatment initiation. In the MS pooled analyses of Study 1 and Study 2, the decline in absolute FEV1 from baseline in patients treated with ZEPOSIA compared to patients who received IFN beta-1a was 60 mL (95% CI: -100, -20) at 12 months. The mean difference in percent predicted FEV1 at 12 months between patients treated with ZEPOSIA and patients who received IFN beta-1a was 1.9% (95% CI: -2.9, -0.8). Dose-dependent reductions in forced vital capacity (FVC) (absolute and % predicted) were also seen at Month 3 in pooled analyses comparing patients treated with ZEPOSIA to patients who received IFN beta-1a [60 mL, 95% CI (-110, -10); 1.4%, 95% CI: (-2.6, -0.2)], though significant reductions were not seen at other timepoints. There is insufficient information to determine the reversibility of the decrease in FEV1 or FVC after drug discontinuation. One patient in MS Study 1 discontinued ZEPOSIA because of dyspnea.

In UC Study 1 the mean difference in decline in absolute FEV1 from baseline in patients treated with ZEPOSIA compared to patients who received placebo was 22 mL (95% CI: -84, 39) at 10 weeks. The mean difference in percent predicted normal (PPN) FEV1 at 10 weeks between patients treated with ZEPOSIA compared to those who received placebo was 0.8% (95% CI: -2.6, 1.0). The difference in reductions in FVC (absolute value and % predicted) seen at Week 10 in UC Study 1, comparing patients who were treated with ZEPOSIA to those who received placebo was 44 mL, 95% CI (-114, 26); 0.5%, 95% CI (-

2.3, 1.2), respectively. There is insufficient information to determine the reversibility of observed decreases in FEV1 or FVC after discontinuation of ZEPOSIA, or whether changes could be progressive with continued use.

Spirometric evaluation of respiratory function should be performed during therapy with ZEPOSIA, if clinically indicated.

Ponesimod

Ponesimod (NDA 213498; Ponvory), an $S1P_1$ receptor modulator, was approved in 2021 for adults with relapsing forms of multiple sclerosis, including clinically isolated syndrome, relapsing-remitting disease and active secondary progressive disease. DPACC was not consulted for ponesimod-related changes in pulmonary function. The current label states under Section 5.3:

"Dose-dependent reductions in FEV1 and reductions in DLCO were observed in PONVORY-treated patients, mostly occurring in the first month after treatment initiation. In Study 1, the reduction from baseline in percent predicted FEV1 at 2 years was 8.3% in PONVORY-treated patients compared to 4.4% in patients receiving teriflunomide 14mg. In Study 1, 7 patients discontinued PONVORY because of pulmonary adverse events. There is insufficient information to determine the reversibility of the decrease in FEV1 or FVC after treatment discontinuation. PONVORY should be used with caution in patients with severe respiratory disease (i.e. pulmonary fibrosis, asthma, and chronic obstructive pulmonary disease). Spirometric evaluation of respiratory function should be performed during therapy with PONVORY if clinically indicated."

III. Table of Studies

Table 1

Trial	Description	Population	Trial Length	Treatment	N
ELEVATE UC 52 APD-334-301	P3 Randomized, double-blind, placebo-controlled safety and efficacy study	≥ 16 years of age with moderately to severely active ulcerative colitis	52 weeks	2 mg PO daily Placebo	289 144
ELEVATE UC 12 APD-334-302	P3 Randomized, double-blind, placebo-controlled safety and efficacy study	≥ 16 years of age with moderately to severely active ulcerative colitis	12 weeks	2 mg PO daily Placebo	238 116

IV. Study Summary APD334-301

Study Overview APD334-301 (ELEVATE UC 52):

Study Design: Phase 3, multicenter, randomized, double-blind, placebo-controlled, safety and efficacy study of etrasimod 2mg in subjects ≥ 16 years of age with moderately to severely active ulcerative colitis. Subjects were randomized 2:1 to study drug or placebo once daily for up to 52 weeks.

Co-Primary Endpoints:

The proportion of subjects achieving clinical remission at Week 12

The proportion of subjects achieving clinical remission at Week 52

Patient Population

Number of Subjects: Randomization of 433 subjects (etrasimod 289; placebo 144), including one subject < 18 years of age.

Key Inclusion Criteria:

- Diagnosed with UC ≥3 months prior to screening confirmed by endoscopy and histology
- Active UC confirmed by endoscopy with ≥10 cm rectal involvement. Subjects with proctitis only who meet other inclusion criteria capped at 15% of total subjects enrolled
- Moderately to severely active UC with MMS of 4 to 9, ES ≥2 and RB ≥1
- Demonstrated inadequate response to, intolerance to at least 1 of the following
    - Oral 5-ASA compound
    - Corticosteroids
    - Thiopurines
    - TNFα antibodies (infliximab, adalimumab, golimumab, biosimilars)
    - Anti-integrin antibodies (vedolizumab)
    - Anti-interleukin 12/23 antibodies (ustekinumab)
    - JAK inhibitors (tofacitinib)

Key Exclusion Criteria

- Severe extensive colitis
    - Physician judgement that the subject was likely to require hospitalization for medical/surgical care for UC within 12 weeks following randomization
    - Current evidence of fulminant colitis, toxic megacolon, or recent history of toxic megacolon, bowel perforation
    - Previous total/partial colectomy
- Crohn's disease, indeterminate colitis, presence or history of a fistula
- Microscopic colitis, ischemic colitis, or infectious colitis

- Hospitalization for exacerbation of UC requiring IV steroids within 12 weeks of screening (a single dose of IV steroids was acceptable)
- Positive assay/stool culture for pathogens (ova and parasite, bacteria) or positive test for *Clostridioides difficile* toxin at screening
- Condition that may affect cardiovascular function
- FEV1 or FVC < 70% of predicted values and FEV_1/FVC < 0.70 at screening
- History of macular edema/retinopathy
- Treatment with ≥3 biologic agents or ≥2 biologics plus a JAK inhibitor approved for treatment of UC

Reviewer Comments: Subjects with airflow limitation were appropriately excluded from the study, but patients with obstructive respiratory disease were not excluded outright.

Pulmonary Function

Safety monitoring included physical examinations, vital signs, laboratory testing (including pregnancy testing), ECGs, adverse events, pulmonary function tests, ophthalmoscopy, tuberculosis screening, and first-dose cardiac monitoring. The overall population underwent PFT monitoring at baseline, Week 12 and Week 52. Subjects with asthma or COPD underwent additional pulmonary function testing at Week 32.

Summary statistics for PFT parameters included change from baseline in absolute and percent predicted forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), FEV1/FVC, total lung capacity (TLC), forced expiratory flow between 25% and 75% of vital capacity (FEF25-75), and corrected diffusing capacity of the lungs for carbon monoxide (DLCO, when available). It is not clear if the Applicant used ATS/ERS criteria for assessment of PFTs.

Pulmonary Results APD334-301

Patient demographics

Patient demographics and medical history are displayed in (**Table 2**).

Table 2 APD334-301 Demographics and Medical History

N (%)	Placebo (n=144) n (%)	Etrasimod 2 mg (n=289) n (%)
Age mean (years)	38.9	41.2
Male	88 (61)	152 (53)
Female	56 (39)	137 (47)
White	129 (90)	256 (89)
Black	3 (2)	6 (2)
Asian	9 (6)	22 (8)
American Indian	3 (2)	1 (0.3)

Not Reported	0	4 (1.4)
Hispanic/Latino	7 (5)	12 (4)
Pertinent Medical History		
History of asthma	6 (4)	11 (4)
History of COPD	0	5 (2)
Chronic bronchitis	1 (0.7)	2 (0.7)
Cough	2 (1.4)	0
Dyspnea	0	2 (0.7)
Interstitial Lung Disease	1 (0.7)	0
Lung Disorder	0	1 (0.3)
Pleural Effusion	0	1 (0.3)
Productive cough	1 (0.7)	0
Pulmonary embolism	1 (0.7)	0
Pulmonary sarcoidosis	0	1 (0.3)
Source: APD334-301 Clinical Study Report Table 6 p. 60 APD334-301 Tables, Figures, and Graphs Table 14.1.5 p. 171		

The average subject in the overall population was 40 years of age, male, and white. The percent of subjects with asthma in the etrasimod group and placebo group are balanced. There were more subjects in the etrasimod group with COPD compared to placebo.

Pulmonary function tests

Pulmonary function tests were performed at baseline, Week 12, and Week 52.

Reviewer comment: An Information Request was sent to clarify why the mean change from baseline values were not equivalent to the timepoint minus the baseline. The Applicant clarified that the mean change from baseline was computed based on the participants with observed measurements at baseline and the timepoint. Because there was attrition throughout the trial, not all participants have measurements at both visits, thus the computation for mean change from baseline does not directly equal the timepoint minus the baseline in all the following tables.

FEV1

The absolute change in FEV1 results were reviewed for Study 301 for the overall population (**Table 3**).

Table 3. APD334-301 Values and Change from Baseline in FEV1 (L) by Visit (Safety Set)

Visit Window	Placebo N= 144	CFBL	Etrasimod 2mg N=289	CFBL	LS Mean Diff 95% Confidence Interval
Baseline					
n	141		284		

Mean (SD)	3.717 (0.9328)		3.522 (0.9537)		
Week 12					
n	120	118	248	244	
Mean (SD)	3.771 (0.9392)	0.010 (0.3274)	3.407 (0.9689)	-0.068 (0.34)	-0.079 (-0.152, -0.005)
Week 52					
n	43	42	153	150	
Mean (SD)	3.555 (0.9265)	-0.092 (0.4479)	3.293 (0.9673)	-0.068 (0.4203)	0.024 (-0.130, 0.178)
Source: Table 14.3.5.3.1 APD334-301 Clinical Study Report Tables, Figures, and Graphs p. 2698 CFBL = change from baseline					

The mean difference between etrasimod and placebo in change from baseline in FEV1 was more pronounced in the etrasimod group at Week 12 (-79 mL) and was nominally significant. However, this difference was not present at Week 52. There was significant attrition in both the etrasimod and placebo groups between Week 12 and Week 52 which limits interpretation of the Week 52 results.

Reviewer Comment: The majority of study discontinuations were due to adverse events. At Week 52, the majority of study discontinuation was due to disease worsening in both arms, but a higher dropout rate occurred in the placebo arm compared to the etrasimod arm. After discussion with DG, this high rate of attrition is not unusual considering this is the first "treat-through" study design that the DG has seen completed and overall, for IBD, drug efficacy remains low.

The changes in percent predicted FEV1 were presented at baseline, Week 12, and Week 52 (**Table 4**).

Table 4. APD334-301 Values and Change from Baseline in % Predicted FEV1 by Visit (Safety Set)

Visit Window	Placebo N=144	CFBL	Etrasimod 2mg N=289	CFBL	LS Mean Diff Confidence Interval
Baseline					
n	141		284		
Mean (SD)	104.298 (17.35)		102.261 (15.5)		
Week 12					
n	120	118	248	244	244
Mean	103.925	0.246	100.060	-1.87 (11.17)	-2.119 (-4.445,

(SD)	(17.13)	(10.22)	(16.56)		0.208)
Week 52					
n	43	42	153	150	150
Mean (SD)	105.256 (18.78)	-0.595 (16.40)	100.412 (17.1182)	-1.533 (12.3134)	-0.938 (-6.399, 4.523)
Source: Table 0029d.1 Information Request April 27, 2023 CFBL= change from baseline					

Although there was a decrease in % predicted FEV1 at both Week 12 and 52, all the mean differences in the change from baseline in percent predicted FEV1 between etrasimod and placebo included the null.

FVC

Changes in FVC were presented at baseline, Week 12, and Week 52 (**Table 5**).

Table 5. APD334-301 Values and Change from Baseline in FVC (L) by Visit (Safety Set)

Visit Window	Placebo N= 144	CFBL	Etrasimod 2mg N=289	CFBL	LS Mean Diff 95% Confidence Interval
Baseline					
n	141		284		
Mean (SD)	4.483 (1.1926)		4.300 (1.2108)		
Week 12					
n	120	118	248	244	
Mean (SD)	4.570 (1.1419)	0.011 (0.5136)	4.216 (1.1879)	-0.030 (0.4887)	-0.040 (-0.152, 0.071)
Week 52					
n	43	42	153	150	
Mean (SD)	4.452 (1.0870)	0.022 (0.5797)	4.046 (1.1163)	-0.050 (0.6413)	-0.072 (-0.279, 0.135)
Source: Table 14.3.5.3.1 APD334-301 Clinical Study Report Tables, Figures, and Graphs p. 2701 CFBL= change from baseline					

The mean difference between etrasimod and placebo in change from baseline in FVC was more pronounced in the etrasimod group at Week 12 (-40 mL) and worsened at Week 52 (-72 ml), however the confidence intervals included the null. Again, there was notable attrition in both the etrasimod and placebo groups between Week 12 and Week 52 limiting the conclusions for Week 52.

Reviewer Comment: Confidence intervals for FEV1 and FVC results were provided via Information Request on March 9, 2023. The Applicant first provided confidence intervals adjusted for factors such as naïve to biologic or JAK inhibitor, baseline disease activity, asthma/COPD at entry, treatment visit, treatment by visit interaction (Information Request March 9, 2023). Unadjusted confidence intervals were then requested and provided via Information Request on March 15, 2023. The unadjusted confidence intervals are included in the tables in this review as these were considered a more accurate reflection of the results and echoed what was reported for other S1P inhibitors in labeling, for example, ozanimod.

In conclusion, there was a nominally significant difference between etrasimod and placebo in the mean change from baseline in FEV1 at Week 12 of -79 ml. Although this difference was not present at Week 52, the Week 52 results are difficult to interpret due to attrition of subjects in both the placebo and etrasimod groups. There were no observable trends in percent predicted FVC, FEV1/FVC, percent predicted FEV1/FVC, TLC, percent predicted TLC, FEF25-75, percent predicted FEF25-75, DLCO, or percent predicted DLCO.

An Information Request was sent to obtain pulmonary function test results and respiratory adverse events in subjects with asthma and COPD. In addition to the baseline, Week 12 and Week 52 PFTs, these subjects also had PFTs performed at Week 32. The results are outlined in **Table 6**.

Asthma and COPD subjects

Table 6. Values and Change from Baseline in FEV1(L) by Visit (Safety Set Asthma and COPD subjects)

Visit Window	Placebo N= 8	CFBL	Etrasimod 2mg N=18	CFBL	LS Mean Difference
Baseline					
n	8		18		
Mean (SD)	3.306 (1.115)		2.901 (0.773)		
Week 12					
n	7		17		
Mean (SD)	3.419 (1.143)	0.076 (0.230)	2.925 (0.736)	-0.036 (0.161)	-0.112
Week 32					
n	1		7		
Mean (SD)	3.010	-0.820	2.986 (0.637)	-0.136 (0.148)	0.684
Week 52					

n	3		9		
Mean (SD)	3.210 (0.830)	0.003 (0.463)	2.499 (0.505)	-0.214 (0.286)	-0.217
Source: Table 0018a.1 APD334-301 Information Request February 8, 2023, p. 1 CFBL= change from baseline					

In subjects with asthma and COPD, the mean difference in change from baseline in FEV1 showed a difference at Week 12 (-112 ml) which was not present at Week 32. A difference was seen again at Week 52 (-217 ml). The interpretability of this data is limited given the small number of subjects in each arm (n=8 placebo and n=18 etrasimod) and attrition in both the placebo and etrasimod groups over time.

Reviewer comment: The number of subjects with asthma and COPD in the Applicant-generated PFT tables do not match the demographic tables from above because the Applicant included several Preferred Terms when generating the PFT tables (asthma, bronchial obstruction, bronchiectasis, bronchitis chronic, COPD, cough variant asthma, emphysema, obstructive airway disorder).

Percent predicted FEV1 and FVC were assessed at baseline, Week 12, Week 32, and Week 52 in asthma and COPD subjects. There were no observable trends in the mean difference in change from baseline between etrasimod and placebo. The interpretability of this data is limited given the small number of subjects in each arm (n=8 placebo and n=18 etrasimod) and attrition in both the placebo and etrasimod groups over time.

Adverse events in subjects with asthma and COPD were reviewed (treatment emergent adverse events, adverse events leading to discontinuation, SAEs, adverse events of special interest), and there were no notable respiratory adverse events in the etrasimod arm compared to placebo.

Pulmonary AEs

There were no respiratory SAEs and no reported AEs leading to death. There were also no respiratory adverse events leading to study drug discontinuation/interruption.

Adverse events were coded using MedDRA v24.1. Severity was classified using the CTCAE v5.0. **Table 7** below contains a summary of the respiratory adverse events that occurred in APD334-301.

Table 7

Summary of Respiratory TEAEs APD334-301

System Organ Class - Preferred Term	Etrasimod 2 mg (N=289) n (%)	Placebo (N=144) n (%)
Respiratory, thoracic and mediastinal disorders	**14 (4.8)**	**8 (5.6)**
Bronchial obstruction	0 (0.0)	1 (0.7)

Summary of Respiratory TEAEs APD334-301

System Organ Class - Preferred Term	Etrasimod 2 mg (N=289) n (%)	Placebo (N=144) n (%)
Cough	2 (0.7)	2 (1.4)
Dyspnea	2 (0.7)	0 (0.0)
Dyspnea exertional	2 (0.7)	0 (0.0)
Epistaxis	0 (0.0)	1 (0.7)
Nasal congestion	1 (0.3)	0 (0.0)
Obstructive airways disorder	1 (0.3)	0 (0.0)
Oropharyngeal pain	1 (0.3)	2 (1.4)
Painful respiration	0 (0.0)	1 (0.7)
Pulmonary mass	1 (0.3)	0 (0.0)
Rhinitis allergic	2 (0.7)	0 (0.0)
Rhinorrhea	4 (1.4)	0 (0.0)
Sinus congestion	0 (0.0)	1 (0.7)
Sneezing	0 (0.0)	1 (0.7)
Wheezing	0 (0.0)	1 (0.7)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "Etrasimod 2 mg" and SAFFL = "Y" (Etrasimod 2 mg); TRT01A = "Placebo" and SAFFL = "Y" (Placebo); TRTEMFL = "Y" and AEBODSYS = "Respiratory, thoracic and medias inal disorders" (Adverse Events).

Generally, the incidence of respiratory adverse events were low and similar across treatment arms. There were slightly more cases of dyspnea and exertional dyspnea in the etrasimod arm (n=2 (0.7%) for each) compared to placebo (n=0).

Pulmonary Adverse Events of Special Interest (AESIs) included airflow obstruction (FEV1, FVC) or decreased gas exchange (DLCO). These were defined as a decrease from baseline in FEV1 or FVC of > 25% or DLCO of > 25% when adjusted for hemoglobin or accompanied by relevant symptoms.

Respiratory AESIs were reviewed and are summarized in (**Table 8**).

Table 8 Pulmonary AESIs

Preferred Term	Placebo n (%)	Etrasimod n (%)
Airflow obstruction (FEV1 or FVC)	1 (0.7)	1 (0.3)
Decreased gas exchange (DLCO)	0	0
Source: Study APD334-301 CSR, Table 40 p. 178		

In the etrasimod subject with airflow obstruction, the AESI was a Grade 1 TEAE of FEV1 decrease that began on Day 88 and did not resolve. No accompanying respiratory symptoms were reported.

In the placebo subject, the AESI was a Grade 1 TEAE of FEV1/FVC that decreased starting on Day 85 but resolved. No accompanying respiratory symptoms were reported.

The Applicant also makes note of the proportion of subjects that experienced >20% declines from baseline in FEV1, FVC, or DLCO (**Table 9).** One etrasimod-treated subject

had an on-treatment FEV1 of < 50% of predicted but did not have a baseline assessment due to COVID-19 restrictions (not shown). No respiratory symptoms were reported.

Table 9. Incidence of Abnormal Pulmonary Function Test Values (Safety Set)

Parameter	**Placebo (N=144) N (%)**	**Etrasimod 2mg (N=289) N (%)**
% Decrease from baseline in FEV1		
n	124	261
>20%	10 (8)	8 (3)
% Decrease from baseline in FVC		
n	124	261
>20%	7 (6)	7 (3)
% Decrease from baseline in DLCO		
n	33	85
>20%	4 (12)	9 (11)

Source: Study APD334-301 CSR Table 48 p. 208

The proportion of subjects that experienced >20% declines from baseline in FEV1, FVC, or DLCO was higher in placebo (FEV1 and FVC) or balanced between groups (DLCO).

Conclusion
Overall, in APD334-301, the FEV1 change from baseline at Week 12 was nominally significant, but no other pulmonary function assessment was significantly different from placebo. Asthma and COPD subjects were included in the study, but the small sample size limited conclusions on pulmonary function effects in this population. Responder analyses for various pulmonary function assessments in the overall population did not demonstrate a difference for etrasimod compared to placebo. A respiratory adverse event safety signal was not identified.

VI. Study Summary APD334-302

Study Overview APD334-302:

Study Design: Phase 3 multicenter, randomized, double-blind, placebo-controlled, safety and efficacy study of etrasimod 2mg in subjects with moderately to severely active ulcerative colitis. Subjects were randomized 2:1 study drug to placebo once daily for up to 12 weeks.

Primary Endpoint:

The proportion of subjects achieving clinical remission at Week 12

Patient Population

Number of Subjects: Randomization of 354 subjects (etrasimod 238; placebo 116)

Key Inclusion and Exclusion Criteria:

Reviewer comment: The inclusion and exclusion criteria for APD334-302 are identical to Study APD334-301.

Pulmonary Function

Safety monitoring includes physical examinations, vital signs, laboratory testing (including pregnancy testing), ECGs, adverse events, pulmonary function tests, ophthalmoscopy, tuberculosis screening, and first-dose cardiac monitoring. The overall population underwent PFT monitoring at baseline and Week 12.

Summary statistics for PFT parameters included change from baseline in absolute and percent predicted forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), FEV1/FVC, total lung capacity (TLC), forced expiratory flow between 25% and 75% of vital capacity (FEF25-75), and corrected diffusing capacity of the lungs for carbon monoxide (DLCO, when available). It is not clear if the Applicant used ATS/ERS criteria for assessment of PFTs.

Pulmonary Results APD334-302

Patient demographics

Patient demographics are displayed in **Table 10**.

Table 10. APD334-302 Demographics and Medical History

N (%)	Placebo (n=116)	Etrasimod 2 mg (n=238)
Age mean (years)	38	40
Male	73 (63)	135 (57)
Female	43 (37)	103 (43)
White	88 (76)	176 (74)
Black	2 (2)	2 (1)
Asian	25 (22)	47 (20)
American Indian	1 (1)	6 (3)
Not Reported	0	6 (3)
Hispanic/Latino	9 (8)	10 (4)
Pertinent Medical History		
History of asthma	7 (6)	9 (4)
History of COPD	2 (2)	1 (0.4)

Bronchiectasis	0	1 (0.4)
Chronic bronchitis	0	1 (0.4)
Cough	0	1 (0.4)
Dyspnea	0	1 (0.4)
Dyspnea exertional	0	1 (0.4)
Eosinophilic pneumonia	0	1 (0.4)
Pleural Effusion	0	1 (0.4)
Pneumothorax	0	2 (1)
Pulmonary fibrosis	0	1 (0.4)
Pulmonary granuloma	1 (1)	0
Sleep apnea syndrome	0	1 (0.4)
Source: APD334-302 Clinical Study Report Table 6 p. 54 APD334-302 Tables, Figures, and Graphs Table 14.1.5 p. 158		

The average subject in the overall population was 38-40 years of age, male, and white. There were more subjects in the placebo group with asthma and COPD.

Pulmonary function tests APD334-302

Pulmonary function tests were performed at baseline and Week 12.

FEV1

The absolute change in FEV1 results were reviewed for Study 302 for the overall population (**Table 11**).

Table 11. Values and Change from Baseline in FEV1(L) by Visit (Safety Set)

Visit Window	Placebo N= 116	CFBL	Etrasimod 2mg N= 238	CFBL	LS Mean Difference Confidence Interval
Baseline					
n	115		238		
Mean (SD)	3.510 (0.8605)		3.505 (0.8275)		
Week 12					
n	101		203		
Mean (SD)	3.481 (0.8121)	-0.062 (0.3759)	3.496 (0.8272)	-0.019 (0.3869)	0.043 (-0.05, 0.13)
Source: Table 14.3.5.3.1 p. 1611 CFBL= change from baseline					

The change in percent predicted FEV1 was reviewed for Study 302 for the overall population (Table 12).

Table 12. Values and Change from Baseline in % Predicted FEV1 by Visit (Safety Set)

Visit Window	Placebo N= 116	CFBL	Etrasimod 2mg N= 238	CFBL	LS Mean Difference
Baseline					
n	115		238		
Mean (SD)	99.8 (16.51)		101.4 (15.53)		
Week 12					
n	101		203		
Mean (SD)	99.4 (16.12)	-1.6 (11.14)	100.9 (17.12)	-0.6 (12.59)	1*
Source: Table 14.3.5.3.1 p. 1612 * 95% CI not requested from the Applicant as the absolute FEV1 change was not significant CFBL= change from baseline					

FVC

The absolute change in FVC results were reviewed for Study 302 for the overall population (**Table 13**).

Table 13. Values and Change from Baseline in FVC by Visit (Safety Set)

Visit Window	Placebo N= 116	CFBL	Etrasimod 2mg N= 238	CFBL	LS Mean Difference 95% Confidence Interval
Baseline					
n	115		238		
Mean (SD)	4.258 (1.0719)		4.260 (0.9581)		
Week 12					
n	101		203		
Mean (SD)	4.263 (0.9787)	-0.031 (0.4482)	4.298 (0.9865)	0.018 (0.4496)	0.049 (-0.06, 0.15)
Source: Table 14.3.5.3.1 p. 1613 *CFBL= change from baseline					

There were no appreciable differences between the change from baseline in FEV1, FVC, or percent predicted FEV1 between etrasimod and placebo in APD334-302. It's unclear why FEV1 declines at Week 12 were demonstrated in Study 301, but not in Study 302. Study 301 was slightly larger, but the study population was similar.

Reviewer comment: The Applicant includes a 2-week follow-up measurement for all PFT parameters however this was only conducted in 1 subject in the etrasimod group. Thus, the results are clinically insignificant and not included in this review.

Asthma and COPD subjects

The absolute change in FEV1 were presented at baseline and Week 12 in asthma and COPD subjects (**Table 14**).

Table 14. Values and Change from Baseline in FEV1(L) by Visit (Safety Set Asthma and COPD subjects)

Visit Window	Placebo N= 9	CFBL	Etrasimod 2mg N=12	CFBL	LS Mean Difference
Baseline					
n	9		12		
Mean (SD)	3.086 (0.740)		2.955 (0.994)		
Week 12					
n	6		9		
Mean (SD)	3.148 (0.552)	-0.042 (0.102)	2.999 (0.987)	-0.112 (0.264)	-0.07
Source: Table 0018a.2 APD334-302 Information Request February 8, 2023 p.1 CFBL= change from baseline					

The difference in change from baseline in absolute FEV1 between etrasimod and placebo was -70 ml at Week 12, however, the interpretability of this data is limited given the small number of subjects in each arm (n=9 placebo and n=12 etrasimod).

The change in percent predicted FEV1 and FVC were assessed at baseline and Week 12 in asthma and COPD subjects. The difference in change from baseline in percent predicted FEV1 between etrasimod and placebo was -11.9% at Week 12. The difference in change from baseline in FVC between etrasimod and placebo was 78 ml at Week 12. The interpretability of this data is limited given the small number of subjects in each arm (n=9 placebo and n=12 etrasimod).

Pulmonary AEs

There were no respiratory AESIs in APD334-302. There were no respiratory SAEs and no reported AEs leading to death. There were also no respiratory adverse events leading to study drug discontinuation/interruption.

Common AEs are outlined in **Table 15**.

Table 15

Summary of TEAEs APD334-302

System Organ Class - Preferred Term	Etrasimod 2 mg (N=238) n (%)	Placebo (N=116) n (%)
Respiratory, thoracic and mediastinal disorders	**3 (1.3)**	**2 (1.7)**
Asthma	0 (0.0)	1 (0.9)
Cough	1 (0.4)	0 (0.0)
Dry throat	0 (0.0)	1 (0.9)
Dyspnea	2 (0.8)	0 (0.0)
Nasal congestion	1 (0.4)	0 (0.0)

Source: OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "Etrasimod 2 mg" and SAFFL = "Y" (Etrasimod 2 mg); TRT01A = "Placebo" and SAFFL = "Y" (Placebo); TRTEMFL = "Y" and AEBODSYS = "Respiratory, thoracic and mediastinal disorders" (Adverse Events).

Similar to Study 301, there were no major trends in respiratory adverse events between the etrasimod and placebo groups. There were slightly more cases of dyspnea in the etrasimod arm (n=2 (0.8%)) compared to placebo (n=0).

The Applicant also makes note of the proportion of subjects that experienced >20% declines from baseline in FEV1, FVC, or DLCO (**Table 16**).

Table 16. Incidence of Abnormal Pulmonary Function Test Values (Safety Set)

Parameter	Placebo (N=116) N (%)	Etrasimod 2mg (N=238) N (%)
% Decrease from baseline in FEV1		
n	102	214
>20%	5 (4.9)	4 (1.9)
% Decrease from baseline in FVC		
n	102	214
>20%	3 (2.9)	2 (0.9)
% Decrease from baseline in DLCO		
n	36	79
>20%	1 (2.8)	6 (7.6)

Source: APD334-302 Study report body Table 38 p. 159

Compared to placebo, fewer subjects in the etrasimod group had a > 20% decrease from baseline in FEV1 or FVC. A larger proportion of subjects in the etrasimod group had a >20% decrease from baseline in DLCO compared with placebo. None of these subjects reported any respiratory symptoms that accompanied the decline in test values. The Applicant also notes that none of the DLCO values were corrected for hemoglobin. Two of the etrasimod subjects had concurrent declines in hemoglobin that would have changed the decrease in DLCO to < 20%. The Applicant also notes that 2 spirometric decreases occurred the day after endoscopy and 1 on the day of endoscopy, where sedation may have interfered with subjects' ability to perform the test.

Conclusion
Overall, there were no pulmonary function assessments that were significantly different from placebo. As in Study 301, asthma and COPD subjects were included in the study, but the small sample size limited conclusions on pulmonary function effects. Responder analysis for various pulmonary function assessments in the overall population did not demonstrate a difference for etrasimod compared to placebo. A respiratory adverse event safety signal was not identified.

VII. Pooled PFT results

The Applicant provides pooled PFT results from Study 301 and 302 in the Integrated Summary of Safety (ISS).

The absolute change in FEV1 results were reviewed for the pooled studies for the overall population (**Table 17**).

Table 17. Values and Change from Baseline in FEV1(L) by Visit (Safety Set Pooled)

Visit Window	Placebo N= 260	CFBL	Etrasimod 2mg N= 527	CFBL	LS Mean Difference Confidence Interval
Baseline					
n	256		522		
Mean (SD)	3.624 (0.9053)		3.514 (0.8976)		
Week 12					
n	223	220	463	459	
Mean (SD)	3.649 (0.8946)	-0.019 (0.3494)	3.440 (0.9001)	-0.049 (0.3635)	-0.030 (-0.087, 0.027)
Week 26					
n	16	15	25	24	
Mean	3.528	-0.196	3.222	-0.066	0.130

(SD)	(0.8294)	(0.6462)	(0.8339)	(0.2314)	(-0.237, 0.497)
Week 52					
n	41	40	159	156	
Mean (SD)	3.521 (0.9343)	-0.108 (0.4528)	3.301 (0.9554)	-0.068 (0.4135)	0.040 (-0.118, 0.198)
Source: ISS Table 14.3.17.1.1 p. 9743 and Response to Information Request March 21, 2023 Table 0029c.1 p.1 CFBL= change from baseline					

The pooled results did not demonstrate a significant difference for etrasimod compared to placebo in change from baseline in absolute FEV1 at any timepoint. The mean difference between etrasimod and placebo in change from baseline in FEV1 was -30 mL at Week 12, however, this difference was not present at other timepoints. There was significant attrition in both the etrasimod and placebo groups between Week 12 and Week 52.

Reviewer comment:
The pivotal pooled PFT results include a Week 26 timepoint because subjects in APD334-301 with pulmonary disease had an additional PFT assessment at Week 32. The Week 32 data were remapped to the Week 26 analysis visits for consistency with all safety data reporting per the statistical analysis plan. Confidence intervals for the pivotal UC pool PFT results were provided via Information Request March 21, 2023.

The change in percent predicted FEV1 results were reviewed for the pooled studies for the overall population (**Table 18**).

Table 18. Values and Change from Baseline in % Predicted FEV1 by Visit (Safety Set)

Visit Window	Placebo N= 260	CFBL	Etrasimod 2mg N= 527	CFBL	LS Mean Difference Confidence Interval
Baseline					
n	256		522		
Mean (SD)	102.281 (17.09)		101.862 (15.5057)		
Week 12					
n	223	220	463	459	
Mean (SD)	102.152 (16.6794)	-0.555 (10.5895)	100.391 (16.8644)	-1.322 (11.7917)	-0.768 (-2.539, 1.003)
Week 26					
n	16	15	25	24	
Mean	98.313	-5.867	95.800	-1.083	4.783

(SD)	(13.6953)	(19.3829)	(19.5661)	(10.7498)	(-6.636, 16.202)
Week 52					
n	41	40	159	156	
Mean (SD)	105.561 (19.1129)	-0.825 (16.7912)	100.484 (16.9877)	-1.571 (12.1247)	-0.746 (-6.424, 4.933)
Source: ISS Table 14.3.17.1.1 p. and Response to Information Request March 21, 2023 Table 0029c.1 p. 3-4 CFBL= change from baseline					

There were no significant differences in change from baseline in percent predicted FEV1 between etrasimod and placebo.

The absolute change in FVC results were reviewed for the pooled studies ELEVATE UC 12 and ELEVATE UC 52 for the overall population (**Table 19**).

Table 19. Values and Change from Baseline in FVC by Visit (Safety Set)

Visit Window	Placebo N= 260	CFBL	Etrasimod 2mg N= 527	CFBL	LS Mean Difference Confidence Interval
Baseline					
n	256		522		
Mean (SD)	4.382 (1.1432)		4.281 (1.1019)		
Week 12					
n	223	220	463	459	
Mean (SD)	4.440 (1.0734)	-0.005 (0.4825)	4.245 (1.0959)	-0.012 (0.4675)	-0.007 (-0.084, 0.070)
Week 26					
n	16	15	25	24	
Mean (SD)	4.378 (1.0966)	-0.140 (0.6690)	4.073 (0.9714)	-0.020 (0.3187)	0.120 (-0.267, 0.508)
Week 52					
n	41	40	159	156	
Mean (SD)	4.395 (1.0812)	0.008 (0.5858)	4.063 (1.1121)	-0.039 (0.6413)	-0.047 (-0.258, 0.165)
Source: ISS Table 14.3.17.1.1 and Response to Information Request March 21, 2023 Table 0029c.1 p.2-3 CFBL= change from baseline					

Although there is a -47 ml difference between the mean change from baseline in FVC between etrasimod and placebo at Week 52, there was significant attrition in both the etrasimod and placebo arms at this time point, and the confidence interval includes the null, rendering this finding not clinically significant.

Reviewer comment: In the Response to Information Request received on April 27, 2023, the Applicant noted that the pivotal pooled results for various PFT measures for Week 52 did not match the individual trial PFT results for ELEVATE UC 52 at Week 52 because there were different definitions of analysis visit windows for Week 52 between the ISS SAP and Study APD334-301 CSR SAP. Additionally, 2 subjects in the placebo group of ELEVATE UC 52 had their Week 52 PFT performed after they received their first dose of etrasimod 2mg in open-label extension study APD334-303, thus per the ISS dataset mapping, they could not contribute to the Week 52 summary for the Pivotal UC Pool.

In conclusion, for the pivotal pooled PFT results which included ELEVATE UC 12 and ELEVATE UC 52, there was a mean difference of -30 ml for FEV1 at Week 12, however, the corresponding confidence interval includes the null.

IX. Labeling Recommendations

Applicant's Proposed Labeling
The Applicant's currently proposed label includes the following in Section 5.9:

Reductions in absolute forced expiratory volume over 1 second (FEV1) (b) (4)

In Section 12.2, the Applicant includes the following language:

(b) (4)

Reviewer comment: (b) (4)

(b) (4)

DPACC Recommendations
DPACC recommends inclusion of the FEV1 changes at Week 12 from Study 301 in the label as this was the only assessment that excluded the null compared to placebo with regards to confidence interval. Study 302 did not demonstrate a nominally significant difference at Week 12, despite the study being in a similar population and size. As such, DPACC also recommends that the results of Study 302 be acknowledged in labeling. The pooled results did not demonstrate a nominally significant difference at Week 12. Including the pooled results alone would not inform prescribers of the risk of a decrease in FEV1 that was seen in Study 301.

Based on DPACC's review of the pulmonary function test results, we recommend that etrasimod include language in Section 5 of the label (in lieu of the Applicant proposed Section 12) to reflect observed changes in FEV1 as outlined below. The recommended label is consistent in content and format to other S1P receptor modulators.

We recommend that Section 5 of the label includes the following language:

Reductions in absolute forced expiratory volume over 1 second (FEV_1) were observed in patients treated with TRADENAME as early as 3 months after treatment initiation. In UC-1, the decline in absolute FEV_1 from baseline in subjects treated with TRADENAME compared to placebo was 79 mL (95% CI: -152, -5) at 3 months. In UC-2, reductions in absolute FEV_1 were not reported. There is insufficient information to determine the reversibility of the decrease in FEV_1 after drug discontinuation. In UC-1 and UC-2, subjects with UC and asthma and/or chronic obstructive pulmonary disease were treated with TRADENAME; however, interpretation of changes in pulmonary function test measures in this population are limited due to small sample sizes.

We recommend Section 12 of the label includes the following language:

Reductions in FEV1 were observed in patients treated with TRADENAME.

We recommend the Highlights Warnings and Precautions includes the following language:

Respiratory Effects: May cause a decline in pulmonary function. Assess pulmonary function (e.g., spirometry) if clinically indicated

Section 17 of the labeling (Patient Counseling) can remain as is:

Advise patients that they should contact their healthcare provider if they experience new onset or worsening dyspnea.

APPEARS THIS WAY ON ORIGINAL

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/

REKHA D JHAMNANI
06/07/2023 10:46:14 AM

MIYA O PATERNITI
06/07/2023 11:09:10 AM

BANU A KARIMI SHAH
06/07/2023 12:11:53 PM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 2, 2023

TO: Jessica Lee, MD
Director
Division of Gastroenterology
Office of Immunology and Inflammation
Office of New Drugs

FROM: Gajendiran Mahadevan, Ph.D.
Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Division Director
DNDSI/OSIS

SUBJECT: Remote regulatory assessment (RRA) of (b) (4) (b) (4) involved with study # APD334-114 submitted in support of NDA 216956 (Etrasimod).

1. RRA Summary

OSIS conducted an remote regulatory assessment (RRA)[1] of the analytical portion of study # APD334-114 (NDA 216956, Etrasimod) performed at (b) (4)

I did not observe any objectionable conditions during the RRA. Therefore, I conclude that analytical data from the reviewed study are reliable.

2. Reviewed Study

Application Number: NDA 216956
Study Number: APD334-114
Study Title: "A phase one, open-label, randomized, single-dose, three-treatment, three-period crossover study in healthy subjects to evaluate the bioequivalence of etrasimod 2 mg proposed commercial and clinical formulations, and to assess the effect of food on the pharmacokinetics of the proposed commercial formulation."

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[1] One set of tools for oversight of regulated products used during the pandemic has been remote regulatory assessments (RRAs). The term "RRA" describes a category of activities for which FDA may use different terminologies, but all are considered to be types of RRAs, including "remote record reviews" and "remote interactive evaluations."

Sample Analysis Period: (b) (4)

3. Scope of RRA

OSIS scientist Gajendiran Mahadevan, Ph.D. reviewed the study mentioned above at (b) (4) (b) (4).

The RRA included opening and close-out meetings with the firm using ZoomGov. Requests for firm documents were made via communication letters. The firm directly uploaded documents in FDA's cloud File Sharing (CFS) service facilitated by Box.com. During the RRA, screen sharing was used to review study data when clarifications were needed.

The current RRA included review of the following items:

-Virtual facility tour of study relevant areas including sample preparation and instrument rooms.
-Study records.
-Method validation.
-Sample analysis.
-Study relevant SOPs.
-Organizational charts.
-Training records of study personnel.
-Floor plans of the facility.

The previous on-site analytical inspection at this firm was conducted in (b) (4) No objectionable conditions were observed and no Form FDA 483 was issued.

4. RRA Observations

At the conclusion of the current RRA, I did not observe any objectionable conditions. No items were discussed with firm's management during the RRA close-out meeting.

Draft: GM 06/01/2023; 06/02/2023
Edit: RCA 06/01/2023; AD 06/01/2023

ECMS: http://ecmsweb.fda.gov/webtop/drl/objectId/0b0026f883b8a1d3
OSIS File BE #: 9775

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/

GAJENDIRAN MAHADEVAN
06/02/2023 10:40:34 AM

RUBEN C AYALA
06/02/2023 10:43:36 AM

ARINDAM DASGUPTA
06/02/2023 10:45:15 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	May 24, 2023
Requesting Office or Division:	Division of Gastroenterology (DG)
Application Type and Number:	NDA 216956
Product Name, Dosage Form, and Strength:	Velsipity (etrasimod) tablets, 2 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Pfizer, Inc. (Pfizer)[a]
FDA Received Date:	October 14, 2022
TTT ID #:	2022-2368
DMEPA 1 Safety Evaluator:	Sherly Abraham, R.Ph.
DMEPA 1 Team Leader:	Idalia Rychlik, Pharm.D.

[a] Shami, Anum. Transfer of NDA ownership from Athena Pharmaceuticals Inc to Pfizer Inc (NDA 216956) Silver Spring (MD): FDA, CDER, OND, DG (US); 2022 DEC 06.

https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af8069f509&showAsPdf=true

1 REASON FOR REVIEW

As part of the approval process for Velsipity (etrasimod) tablets, the Division of Gastroenterology (DG) requested that we review the proposed Velsipity prescribing information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS 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-N/A
ISMP Newsletters*	C-N/A
FDA Adverse Event Reporting System (FAERS)*	D-N/A
Labels and Labeling	F

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

3 CONCLUSION AND RECOMMENDATIONS

The proposed prescribing information (PI), container labels, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for Pfizer, Inc(Pfizer).

4 RECOMMEDATIONS FOR DIVISION OF GASTROENTEROLOGY (DG)

Table 2. Identified Issues and Recommendations for Division of Gastroenterology (DG)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information-General Issues			
1.	As currently displayed, the place holder, “TRADENAME”, is used	Proposed proprietary name, Velsipity, was found conditionally acceptable by	Replace the “Tradename” with approved name, “Velsipity” throughout the PI.

	instead of the conditionally approved name, “Velsipity” throughout the prescribing information (PI).	DMEPA 1 on January 9, 2023 under IND 125154 and NDA 216956.	Proposed proprietary name, Velsipity, was found conditionally acceptable by DMEPA 1 on January 9, 2023 under IND 125154 and NDA 216956.
Full Prescribing Information – Section 2 Dosage and Administration			
1.	The title of subsection 2.1 is missing information on medications and vaccination.	Lack of comprehensive information in subsection title in Dosage and Administration may cause health care providers to overlook important information on medications and vaccination.	Revise the subsection 2.1 title to accurately reflect all the information included in the subsection. For example: Assessments, Medications, and Vaccination Prior to First Dose of TRADENAME
2.	The statements under ‘Recommended Dosage’ Subsection 2.2 lack readability.	Lack of readability may lead to confusion of medication administration for the healthcare providers.	Consider utilizing bullets to enhance the visibility of important information. For example, • The recommended dose of TRADENAME is 2 mg taken orally once daily. • Swallow the tablet whole, with or without food *[see Clinical Pharmacology (12.3)]*.
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	The imprint code is missing.	21 CFR 201.57(c)(17)	We recommend adding the imprint code to the How Supplied/Storage and Handling section in the PI labeling to facilitate product identification.
Medication Guide (MG)			
1.	The storage statement is missing the excursion	Inconsistencies between PI and MG may lead to	Revise the storage statement to align between MG and PI.

	storage information.	confusion of storage information of the product.	

5 RECOMMENDATIONS FOR PFIZER, INC(PFIZER)

Table 3. Identified Issues and Recommendations for Pfizer, Inc(Pfizer) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s), Carton Labeling, and Sample Wallet			
1.	The manufacturer name [Pfizer] on the Principal Display Panel competes in prominence from critical product information [e.g., (proprietary name)]	Critical product information such as the proprietary name should appear as the most prominent information on the principal display panel in accordance with 21 CFR 201.15.	We recommend to remove the manufacturer name (“Pfizer”) from the PDP as it is already present on the back panel.
2.	The statement of strength is followed by an asterisk (*).	The asterisk is unnecessary and distracting.	Delete the asterisk from the strength statement.
3.	The terminology within the Recommended Dosage statement [(i.e., “DOSAGE AND USE See accompanying prescribing information”)] is inconsistent with the terminology in the Prescribing Information.	To ensure consistency with the terminology in the Prescribing Information.	We recommend revising the recommended dosage statement to read, “Recommended dosage: see Prescribing Information.” and remove the bolded font.
4.	The storage statement on the side panel is bolded.	Overuse of bold font may diminish its effect on prominence for other important product information on the PDP.	We recommend to remove the bolded font from the storage statement on the side panel.
5.	We note the inclusion of a medication guide (MG) as part of the labeling submission; however, the MG statement is	Per 21 CFR 208.24(d), the label of each container or package, where the container label is too small, of drug product for which a	Ensure the Medication Guide statement appears in accordance with 21 CFR 208.24(d).

Table 3. Identified Issues and Recommendations for Pfizer, Inc(Pfizer) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	missing from the principal display panel of the container label and carton labeling.	Medication Guide is required under this part shall instruct the authorized dispenser to provide a Medication Guide to each patient to whom the drug product is dispensed, and shall state how the Medication Guide is provided. These statements shall appear on the label in a prominent and conspicuous manner.	
6.	The format for expiration date is incorrect.	Clearly defining the expiration date will minimize confusion and risk for deteriorated drug medication errors.	Revise the expiration date format as described below. 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

Table 3. Identified Issues and Recommendations for Pfizer, Inc(Pfizer) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			separate the portions of the expiration date.
Carton Labeling			
1.	It is unclear where the machine-readable product identifier is located on the label.	The Drug Supply Chain Security Act (DSCSA) requires, for certain prescription products, that the smallest saleable unit display a human-readable and machine-readable (2D data matrix barcode) product identifier.	The DSCSA guidance on product identifiers recommends a machine-readable (2D data matrix barcode) product identifier and a human-readable product identifier. . Include the machine-readable data matrix barcode to the carton labeling. The guidance also recommends the format of the human-readable portion be located near the 2D data matrix barcode as the following: NDC: [insert NDC] SERIAL: [insert serial number] LOT: [insert lot number] EXP: [insert expiration date] We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf.

Table 3. Identified Issues and Recommendations for Pfizer, Inc(Pfizer) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Sample Wallet Card			
1.	It is not immediately clear what the designated strength is (b) (4)	Failure to clearly express the product strength in "2 milligram per tablet" may lead to wrong dose errors.	We recommend revising the strength statement ["2 mg" to state "2 mg per tablet"] to make it clear that the designated strength is per unit so there is no confusion as to how much product is contained (b) (4) See *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).*

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Velsipity that Pfizer, Inc(Pfizer) submitted on October 14, 2022.

Table 4. Relevant Product Information for Velsipity	
Initial Approval Date	N/A
Active Ingredient	etrasimod
Indication	treatment of (b) (4) moderately to severely active ulcerative colitis (UC).
Route of Administration	oral
Dosage Form	tablets
Strength	2 mg
Dose and Frequency	2 mg taken orally once daily
How Supplied	30 count bottle
Storage	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].
Container Closure	Bottle: 100 mL high-density polyethylene (HDPE) bottle closed with polypropylene cap that has 4 g desiccant (silica gel) integrated directly into the cap. (b) (4)

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Velsipity labels and labeling submitted by Pfizer, Inc(Pfizer).

- Container Label(s) received on October 14, 2022
- Carton Labeling received on October 14, 2022
- Professional Sample Wallet card received on October 14, 2022
- Professional Sample Carton Labeling received on October 14, 2022
- Professional Bottle Label received on October 14, 2022
- PI and Medication Guide received on October 14, 2022
  \\CDSESUB1\EVSPROD\nda216956\0001\m1\us\draft-labeling-text-pkg-insert.docx

F.2 Label and Labeling Images

Container label(s)

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

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

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/

SHERLY ABRAHAM
05/24/2023 03:59:56 PM

IDALIA E RYCHLIK
05/24/2023 04:05:22 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic
and Reproductive Medicine
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Division of Pediatrics and Maternal Health Review

Date: 5/5/2023 **Date consulted:** 10/18/2022

From: Katherine Kratz, M.D., Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health (DPMH)

Through: Miriam Dinatale, D.O., Team Leader, Maternal Health, DPMH

Lynne P. Yao, MD, OND, Division Director, DPMH

To: Division of Gastroenterology (DG)

Drug: Etrasimod (APD334)

NDA: 216956/S-023

Applicant: Pfizer, Inc.

Subject: Pregnancy and Lactation Labeling

Indication: Treatment of moderately to severely active ulcerative colitis (UC) in adults

Materials Reviewed:

- DPMH consult request dated 10/18/2022. DARRTS Reference ID 5063389.
- Applicant's submitted background package and proposed labeling for NDA 216596, Sequence Number (SN) 0001.
- DPMH Maternal Health-Epidemiology Integrated Review of Post-marketing Requirement (PMR) 1679-3 Pregnancy Registry 11th Annual Interim Report and Pregnancy Outcomes Intensive Monitoring (PRIM) 8th Interim Report for Gilenya (fingolimod), NDA 022527, by Jane Liedtka, M.D. and Silvia Perez-Vilar, Ph.D., Pharm.D., dated 11/22/2022. DARRTS Reference ID: 5081845.

- DPMH Review of Post-marketing Requirement (PMR) 1679-3 Pregnancy Registry Eighth Interim Report and Pregnancy Outcomes Intensive Monitoring (PRIM) Fifth Interim Report, Prior approval labeling supplement (PAS) #29 for Gilenya (fingolimod), NDA 22527, by Jane Liedtka, M.D., dated 12/9/2019. DARRTS Reference ID: 4528584.
- DPMH Labeling Review for Gilenya (fingolimod), NDA 022527, by Richardae Araojo, PharmD, dated 9/20/2010. No DARRTS Reference ID noted.
- DPMH Post-Marketing Requirement (PMR) Memo for Zeposia (ozanimod), NDA 209899, by, Wenjie Sun, M.D., dated 3/5/2021. DARRTS Reference ID: 4757744.
- Maternal Health-Epidemiology-Biometrics Pregnancy Registry Protocol Review for Mayzent (siponimod), IND 76122, by Leyla Sahin, M.D., Silvia Perez-Vilar, PharmD, Ph.D., Kira Leishear, Ph.D., MS, Ben Wong, Ph.D., Yueqin Zhao, Ph.D., dated 7/31/2020. DARRTS Reference ID: 4649912.
- United States Prescribing Information (USPI) for GILENYA (fingolimod) capsules.
- USPI for MAYZENT (siponimod) tablets.
- USPI for ZEPOSIA (ozanimod) capsules.
- USPI for PONVORY (ponesimod) tablets.

Consult Question: "We request DPMH review of the NDA 216956 labeling (PI and med guide)."

I. INTRODUCTION AND BACKGROUND

On October 14, 2022, the applicant, Pfizer, Inc., submitted a 505(b)(1) New Drug Application (NDA) for a new molecular entity (NME), etrasimod, which is a sphingosine 1-phosphate (S1P) receptor modulator developed as a once-daily oral medication for treatment of moderately to severely active UC in adults. The Division of Gastroenterology (DG) consulted DPMH on October 18, 2022 to assist with the Pregnancy and Lactation subsections of labeling.

Relevant Regulatory History

- The S1P receptor plays an important role in embryogenesis, including vascular and neural development.[1]

- 2010: The first S1P receptor modulator, Gilenya (fingolimod/ S1P1,3,4,5 receptor modulator), was approved. This is the only S1P receptor modulator for which DPMH was consulted to review labeling and to provide recommendations for postmarketing requirements (PMRs) at the time of the original NDA submission. At the time of approval, DPMH recommended a pregnancy exposure registry for Gilenya. An enhanced pharmacovigilance program called Pregnancy Outcomes Intensive Monitoring (PRIM) to prospectively capture outcomes following Gilenya exposure in pregnancy that are not captured by the Gilenya Pregnancy Registry (GPR) was initiated in 2014. The most recent

[1] DPMH Post-Marketing Requirement Memo for Zeposia (ozanimod), NDA 209899, by, Wenjie Sun, M.D., dated March 5, 2021. DARRTS Reference ID: 4757744.

FDA review of the GPR and PRIM interim reports[2] included the following analyses and conclusion:

- GPR analysis: "crude estimates for MCMs [major congenital malformations] from the GPR show higher (>3- fold) prevalence rates of major malformations in exposed patients when compared to both the EUROCAT and MACDP data. Overall, the point estimates are also higher compared to those in unexposed women with MS or in women exposed to fingolimod or to other drugs approved to treat MS (glatiramer acetate, natalizumab, and interferon) reported in the literature provided by the Sponsor and appear to be higher (>2.4-fold) than those from the FDA's Sentinel analyses."

- PRIM analysis: "In prospective PRIM cases, which include a sample size significantly greater than the GPR (n=525 vs. 184), the MCM rate was 2.9%, which is consistent with the general background rate. The prevalence of congenital heart defects (1.51%; 95% CI: 0.66, 2.96) was higher than would be expected compared to the EUROCAT reference (0.81%; 95% CI: 0.80, 0.81), but with overlapping confidence intervals."

- FDA conclusion: "it may be premature to consider a definitive statement regarding an increase in MCMs associated with use of Gilenya during pregnancy based on interim results from a descriptive registry without an internal comparison group, and PRIM data that have not indicated an increased risk of MCMs overall."

- 2019-2021: Three additional S1P receptor modulators were approved. DPMH was consulted after approval of these three S1P receptor modulators listed below to review PMRs that had been issued by the primary review division.

  - Mayzent (siponimod/ S1P1,5 receptor modulator) was approved on 3/26/2019 with a PMR for a pregnancy exposure registry.

  - Zeposia (ozanimod/S1P1,5 receptor modulator) approved on 3/25/2020 with PMRs for a pregnancy exposure registry and a complementary database study.

  - Ponvory (ponesimod/S1P1 receptor modulator) approved on 3/18/2021 with PMRs for a pregnancy registry study and a complementary database study.

- Among the S1P receptor modulators, only Zeposia (ozanimod) is approved for the treatment of UC. The other S1P receptor modulators listed above are approved for the treatment of multiple sclerosis (MS).

[2] DPMH Maternal Health-Epidemiology Integrated Review of Post-marketing Requirement (PMR) 1679-3 Pregnancy Registry 11th Annual Interim Report and Pregnancy Outcomes Intensive Monitoring (PRIM) 8th Interim Report for Gilenya (fingolimod), NDA 22527, by Jane Liedtka, M.D. and Silvia Perez-Vilar, Ph.D., Pharm.D., dated 11/22/2022. DARRTS Reference ID: 5081845.

Drug Characteristics[3]

Drug class	S1P receptor modulator
Mechanism of action	• Binds with high affinity to S1P receptors 1, 4, and 5 ($S1P_{1,4,5}$) (b) (4) • Partially and reversibly blocks the capacity of lymphocytes to egress from lymphoid organs, reducing the number of lymphocytes in peripheral blood (b) (4)
Dosage form/dosing	2 mg tablet/take orally once daily
Molecular weight	631.69 g/mol
Half-life	30 hours
% protein bound	97.9%
Bioavailability	Not specified

II. REVIEW

PREGNANCY

UC and Pregnancy[4]

UC in pregnancy has been previously described by DMPH.[1] Briefly, the risk of poor pregnancy outcomes in patients with UC is greatest in those who have active disease at the time of conception. Poor pregnancy outcomes include antepartum hemorrhage, preterm delivery, and low birth weight infants. The risk of congenital abnormalities does not appear to be increased in patients with UC.

Nonclinical Experience

In the embryo-fetal development studies in rats and rabbits, administration of etrasimod during pregnancy produced embryolethality at 4 mg/kg/day, which was not observed at doses of 1 or 2 mg/kg/day. Fetal malformations were noted as follows:[5]

- Rats:
    - Etrasimod-related external fetal malformations: localized fetal edema, fetal anasarca, meningocele, short tail, and spina bifida were noted at ≥ 4 mg/kg/day. No external fetal malformations were noted in rats at 2 mg/kg/day.
    - Etrasimod-related visceral malformations: aortic arch, aorticopulmonary septal defect, and interventricular septal defect as well as a developmental variation of short brachiocephalic trunk were noted ≥ 1 mg/kg/day.

[3] Applicant's submitted background package, Module 1.14.1.2, Annotated Draft Labeling Text, SN 0001; under review by DG.
[4] Peppercorn, M et al. Fertility, pregnancy, and nursing in inflammatory bowel disease. UpToDate. Topic 4083 Version 54.0. Accessed 5/3/2023.
[5] Applicant's submitted background package, Module 2.4, Nonclinical Overview, page 18 and Module 2.6.6, Toxicology Written Summary, page 47.

- Rabbits:

    - Etrasimod-related visceral malformations: aortic arch and skeletal variations were noted ≥ 10 mg/kg/day; fused sternebrae and carpal flexure were also noted at 20 and 25 mg/kg/day, respectively. No etrasimod-related malformations or developmental variations were noted in rabbits at 2 mg/kg/day.

- NOAELs:
    - Based on these findings, the NOAELs for embryo-fetal development were < 1 mg/kg/day and 2 mg/kg/day in rats and rabbits, respectively, as shown in this applicant-provided table:[6]

Table 2: NOAELs and Exposure Margins for Oral Etrasimod in Reproductive and Development Toxicity Studies

Toxicity Study	NOAEL (mg/kg/day)	AUC (µg·h/mL)[a]		Exposure Margin[b]	
		M	F	M	F
Oral Embryo-fetal Developmental					
Maternal toxicity in pregnant Sprague Dawley rats	4	NA	45[d]	NA	21[e]
Embryo-fetal toxicity in pregnant Sprague Dawley rats	< 1	NA	11[d]	NA	< 5[e]
Maternal toxicity in pregnant New Zealand White rabbits	20	NA	24[f]	NA	11[g]
Embryo-fetal toxicity in pregnant New Zealand White rabbits	2	NA	1.70[f]	NA	0.8[g]

[a] AUC values were obtained at/near termination (ie, steady-state), or as specified.
[b] The safety margin was determined based on the ratio of mean plasma systemic exposure (AUC0-24 or AUC0-last) values determined at steady state in the specified nonclinical toxicity study to the mean steady-state plasma AUC(0-τ) value from 2 mg once daily dosing of etrasimod in clinical Study APD334-002 in healthy normal subjects (2.162 µg·h/mL).
[d] Maternal exposure on Gestational Day 17.
[e] Exposure margin was calculated from the maternal AUC exposure on Gestational Day 17 and the mean steady-state AUC0-24 in healthy volunteers of 2.162 µg·h/mL.
[f] Maternal exposure on Gestational Day 20.
[g] Exposure margin was calculated from the maternal AUC exposure on Gestational Day 20 and the mean steady-state AUC0-24 in healthy volunteers of 2.162 µg·h/mL.

The reader is referred to the full Pharmacology/Toxicology review by Sarah Morgan, Ph.D.

Review of Clinical Trials

Throughout the etrasimod clinical development program, pregnant and lactating females were excluded from study participation. Females of reproductive potential were to use

[6] Applicant's submitted background package, Module 2.4, Nonclinical Overview, page 19.

effective contraception methods during treatment and for at least 30 days after their last dose. Hormonal/barrier/abstinence contraception methods were permitted. Male subjects with a pregnant or non-pregnant female of childbearing potential partner were to use condoms during treatment and for 30 days following treatment. Females who became pregnant during an etrasimod study were required to discontinue study treatment.[7]

In the etrasimod clinical program, there were a total of 8 pregnancies as of January 31, 2022. Pregnancies occurred in the following subjects:[7]

- Seven female subjects who received etrasimod 2 mg (5 subjects for UC; 2 for atopic dermatitis).
- One female partner of a male subject who received etrasimod 2 mg (for UC).

The outcomes of the pregnancies are as follows:

- 3 pregnancies are ongoing
- 2 pregnancies resulted in elective terminations
- 2 pregnancies resulted in spontaneous abortions in the first trimester
- 1 pregnancy was an ectopic pregnancy

Reviewer comment:
Based on the nonclinical data, etrasimod may cause embryolethality or fetal neural, cardiac, and/or skeletal malformations. The data on pregnancy during the clinical trials are insufficient to inform the risk of maternal, fetal, and infant outcomes associated with the use of etrasimod during pregnancy.

Review of Literature

S1P receptor modulators as a class[8]

There are five S1P receptors (S1PRs): S1PR 1-5. S1PRs are involved in the regulation of lymphocyte trafficking, brain and cardiac function, vascular permeability, and vascular and bronchial tone. SIP receptor modulators bind to different S1P receptors. Fingolimod has broad receptor affinity (S1PR1, 3, 4, and 5), whereas subsequently developed S1PR modulators are more specific. Siponimod and ozanimod are selective modulators of S1PR1 and S1PR5, and ponesimod is specific for S1PR1.

Animal studies[9,10,11,12] for all S1PR modulators have demonstrated embryolethality and developmental toxicity. Developmental toxicities for fingolimod involved cardiac malformations. Developmental toxicities for siponimod and ponesimod involved skeletal and visceral malformations. For ozanimod, developmental toxicities included skeletal and vascular

[7] Applicant's submitted background package, Module 2.5, Clinical Overview, page 87.
[8] McGinley MP, Cohen JA. Sphingosine 1-phosphate receptor modulators in multiple sclerosis and other conditions. Lancet. 2021 Sep 25;398(10306):1184-1194. doi: 10.1016/S0140-6736(21)00244-0. Epub 2021 Jun 24. Erratum in: Lancet. 2021 Sep 25;398(10306):1132. PMID: 34175020.
[9] USPI for GILENYA (fingolimod) capsules.
[10] USPI for MAYZENT (siponimod) tablets.
[11] USPI for ZEPOSIA (ozanimod) capsules.
[12] USPI for PONVORY (ponesimod) tablets.

abnormalities and neurobehavioral changes. These developmental toxicities occurred in the absence of maternal toxicity.

Applicant's review:
There are no adequate and well-controlled studies on the embryonic developmental risk associated with the use of etrasimod in pregnant women.[13]

DPMH review:
DPMH conducted a search of published human studies in PubMed and Embase, using the search terms "sphingosine 1-phosphate receptor modulator" OR "etrasimod" OR "siponimod" OR "ozanimod" OR "ponesimod" OR "fingolimod" AND "pregnancy," "pregnancy outcomes," "birth defects," "stillbirth," and "spontaneous abortion." No relevant publications were found related to siponimod, ozanimod, or ponesimod. The following publication related to fingolimod was identified:

- Fingolimod:
    - Platzbecker et al.[14] conducted a claims database study using the German Pharmacoepidemiological Research Database (GePaRD, which contains claims data from ~20% of the German population). Between 2011-2019, the authors identified 136 pregnancies exposed during early pregnancy to fingolimod. Among the 136 pregnancies, 85 (72%) ended in live birth, 10 (8%) in an induced abortion, and 4 (3%) in a spontaneous abortion. Outcomes were unknown for 17 (14%) pregnancies. Among the 85 pregnancies that resulted in live birth, mother-newborn linkage was successful in 64 cases. Six (9%) of the fingolimod-exposed infants had major congenital malformations (MCMs) as follows: 4 cardiac defects, 1 limb abnormality, 1 with a cardiac defect + microcephaly. The authors stated that their findings support the concern that fingolimod is harmful for children exposed during pregnancy as the proportion of children exposed to fingolimod with heart defects "was more than 10 times higher than the proportion expected based on data from EUROCAT (~0.6% of live births with heart defects in 2019)." The authors noted the limitations of a claims-based study and concluded that their study was descriptive in nature only and not designed to estimate causality.

Reviewer comment:
The descriptive data presented by Platzbecker et al. raise a concern for a potential signal for teratogenicity for fingolimod; however, conclusions cannot be drawn from these data due to the limitations of the study design. FDA continues to monitor the Gilenya

[13] Applicant's submitted background package, Module 2.5, Clinical Overview, page 87 and Module 2.7.4 Summary of Clinical Safety page 267.
[14] Platzbecker K, Wentzell N, Kollhorst B, Haug U. Fingolimod, teriflunomide and cladribine for the treatment of multiple sclerosis in women of childbearing age: description of drug utilization and exposed pregnancies in Germany. Mult Scler Relat Disord. 2022 Nov;67:104184. doi: 10.1016/j.msard.2022.104184. Epub 2022 Sep 14. PMID: 36174258.

Pregnancy Registry and PRIM for a teratogenicity signal.[15] Due to the potential for teratogenicity, subsection 8.3 of Gilenya labeling was updated to include a pregnancy testing recommendation in December 2019.

DPMH also searched Micromedex,[16] Reprotox,[17] TERIS,[18] and Shepard's[19] for "etrasimod" and "sphingosine 1-phosphate (S1P) receptor modulator." As expected for this NME, no information was retrieved related to etrasimod. No novel information was found related to approved S1P receptor modulators.

LACTATION

Nonclinical Experience

When etrasimod was orally administered to female rats during pregnancy and lactation, etrasimod was detected in the plasma of the offspring, suggesting excretion of etrasimod in milk.[20]

The reader is referred to the full Pharmacology/Toxicology review by Sarah Morgan, Ph.D.

Review of Clinical Trials

There are no lactation data from clinical trials.

Review of Literature

S1P receptor modulators as a class [9,10,11,12]

S1P receptor modulators are excreted in the milk of rats. There are no data on the presence of S1P receptor modulators in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. Labeling for other S1P receptor modulators has included the standard benefit/risk statement: The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRADENAME and any potential adverse effects on the breastfed infant from TRADENAME or from the underlying maternal condition.

Applicant's review:

There are no data on the presence of etrasimod in human milk or the effects of etrasimod on the breastfed infant or on milk production.[21]

DPMH review:

DPMH conducted a search for published human studies in PubMed and Embase, using the search terms: "sphingosine 1-phosphate receptor modulator" OR "etrasimod" OR "siponimod"

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[15] DPMH Maternal Health-Epidemiology Integrated Review of Post-marketing Requirement (PMR) 1679-3 Pregnancy Registry 11th Annual Interim Report and Pregnancy Outcomes Intensive Monitoring (PRIM) 8th Interim Report for Gilenya (fingolimod), NDA 22527, by Jane Liedtka, M.D. and Silvia Perez-Vilar, Ph.D., Pharm.D., dated 11/22/2022. DARRTS Reference ID: 5081845.

[16] Truven Health Analytics information, http://www.micromedexsolutions.com. Accessed 3/14/2023.

[17] Reprotox Website: www.Reprotox.org. Accessed 3/14/2023.

[18] TERIS database, Truven Health Analytics, Micromedex Solutions. Accessed 3/14/2023.

[19] Shepard's database, Truven Health Analytics, Micromedex Solutions. Accessed 3/14/2023.

[20] Applicant's submitted background package, Module 2.5, Clinical Overview, page 87.

[21] Applicant's submitted background package, Module 2.5, Clinical Overview, page 87.

OR “ozanimod” OR “ponesimod” OR “fingolimod” AND “lactation” and “breastfeeding.” No relevant publications were found.

In addition, DPMH conducted a search for sphingosine 1-phosphate receptor modulators in Micromedex, Hale’s *Medications and Mothers’ Milk*,[22] Reprotox, the Drugs and Lactation Database (LactMed),[23] and Briggs *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk.*[24] No novel information was found on lactation related to approved S1P receptor modulators.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

In a bacterial reverse mutation assay, etrasimod was negative for mutagenic activity in all bacterial tester strains, both with and without metabolic activation. Further, etrasimod was considered non-clastogenic/aneugenic in the in vitro chromosome aberration assay under all treatment conditions tested. Based on a weight of evidence assessment, which includes a negative in vitro genetic toxicology battery and evidence of bone marrow toxicity at the high dose (300 mg/kg/day) in the in vivo micronucleus assay, etrasimod is not considered genotoxic in rats or to pose a genotoxic risk to humans.[25]

Administration of etrasimod (≤ 20 mg/kg/day) produced no test article-related tumorigenic effects in rats, but resulted in an oncogenic effect (increased incidence of hemangiosarcoma or hemangiomas) in mice at doses ≥ 6 mg/kg/day. This effect is consistent with the class effect observed with approved S1P receptor modulators (Gilenya, Mayzent, Zeposia, and Ponvory).[26]

There were no etrasimod-related effects on spermatogenesis or fertility in males at any dose level evaluated. In addition, there were no etrasimod-related effects on fertility or early embryonic development in females at any dose level evaluated. The NOAELs for fertility and early embryonic development were considered to be 200 mg/kg/day for males and 4 mg/kg/day for females, and extrapolated to approximately 467 × and 21 × the human exposure at 2 mg/day.[27]

The reader is referred to the full Pharmacology/Toxicology review by Sarah Morgan, Ph.D.

Review of Clinical Trials

There were no clinically relevant pharmacokinetic (PK) or pharmacodynamic (PD) interactions between a monophasic oral contraceptive containing ethinyl estradiol (EE) and levonorgestrel (LNG) and etrasimod in a phase 1 study (study APD334-111). The applicant stated that

[22] Hale, Thomas W. Hale’s Medications & Mothers’ Milk 2021: A Manual of Lactational Pharmacology. 19th ed. New York: Springer Publishing Company, 2020. www halesmeds.com
[23] Drugs and Lactation Database (LactMed). Accessed 3/14/2023.
[24] Briggs, Gerald G., Craig V. Towers, and Alicia B. Forinash. Briggs Drugs in Pregnancy and Lactation: a Reference Guide to Fetal and Neonatal Risk. 12th edition. Philadelphia, PA: Lippincott Williams & Wilkins, 2021. Print.
[25] Applicant’s submitted background package, Module 2.4, Nonclinical Overview, pages 16-17.
[26] Applicant’s submitted background package, Module 2.4, Nonclinical Overview, page 17.
[27] Applicant’s submitted background package, Module 2.4, Nonclinical Overview, page 18.

"concomitant use of etrasimod is not expected to decrease the efficacy of hormonal contraceptives."[28]

Review of Literature

S1P receptor modulators as a class[9,10,11,12]

For all approved S1P receptor modulators, effective contraception is recommended during and after treatment until elimination of the drug has occurred (i.e., for 5-6 half-lives after the last dose of the drug).

Applicant's review:

The effect of etrasimod on human fertility has not been evaluated.[29]

DPMH review:

DPMH conducted a literature search for studies in humans using PubMed and Embase, using the search terms "sphingosine 1-phosphate receptor modulator" OR "etrasimod" OR "siponimod" OR "ozanimod" OR "ponesimod" OR "fingolimod" AND "fertility," "contraception," "oral contraceptives," and "infertility." DPMH also conducted a search in Micromedex, Reprotox, and TERIS.[30] One relevant publication was found:

- David et al.[31] conducted a PK study in which 31 healthy women received a combined oral contraceptive (EE + LNG) on days 1-14, followed by the oral contraceptive + fingolimod on days 15-28. The authors reported that the pharmacokinetics of EE were unchanged in the presence of fingolimod. The LNG maximum plasma concentration at steady state and the area under the concentration-time curve during a dosing interval increased. The authors concluded that fingolimod does not alter the pharmacokinetics of a combined oral contraceptive containing EE and LNG.

  Reviewer comment:
  The nonclinical data suggest that etrasimod does not affect fertility. The limited clinical data from the phase 1 study and the publication by David et al. suggest that S1P receptor modulators do not reduce the efficacy of combined oral contraceptives.

III. DISCUSSION AND CONCLUSIONS

Pregnancy

Eight human pregnancies have been described in the clinical development program for etrasimod. These pregnancies do not provide adequate information about the fetal or maternal risks associated with etrasimod exposure during pregnancy. Nonclinical data suggest fetal risks of demise or neural, cardiac, and/or skeletal malformations with exposure to etrasimod in utero. Based on animal studies and the mechanism of action for this S1P receptor modulator and all

[28] Applicant's submitted background package, Module 2.7.2, Summary of Clinical Pharmacology Studies, page 128.
[29] Applicant's submitted background package, Module 2.5, Clinical Overview, page 88.
[30] TERIS database, Truven Health Analytics, Micromedex Solutions. Accessed 3/14/2023.
[31] David OJ, Ocwieja M, Meiser K, Emotte C, Jakab A, Wemer J, den Daas I, Schmouder R. Pharmacokinetics of fingolimod (FTY720) and a combined oral contraceptive coadministered in healthy women: drug-drug interaction study results. Int J Clin Pharmacol Ther. 2012 Aug;50(8):540-4. doi: 10.5414/CP201675. PMID: 22735460.

others that have been approved, DPMH recommends including text in labeling about the possibility of fetal harm in section 5 under "Embryofetal Toxicity," and in subsection 8.1 under "Risk Summary" and "Animal Data."

DPMH recommends a Clinical Considerations section for Disease-Associated Maternal and/or Embryo/Fetal Risk to inform prescribers of the risks in pregnancy associated with increased UC disease activity. The following language has been used for other drugs indicated to treat UC and is recommended for etrasimod: "Published data suggest that the risk of adverse pregnancy outcomes in women with inflammatory bowel disease (IBD) is associated with increased disease activity. Adverse pregnancy outcomes include preterm delivery (before 37 weeks of gestation), low birth weight (less than 2500 g) infants, and small for gestational age at birth."

Due to the potential risks to the fetus of etrasimod use during pregnancy, females of reproductive potential should use effective contraception while taking etrasimod and for 5-6 half-lives after stopping etrasimod and this information should appear in the labeling under section 5, "Fetal Risk," and subsection 8.3, "Females and Males of Reproductive Potential." DPMH discussed the specific duration for which effective contraception should be used after stopping etrasimod with the DG Clinical Pharmacology Team. The DG Clinical Pharmacology Team recommended specifying 7 days to represent 5-6 half-lives (30-hour half-life x 5-6 half-lives).

Because etrasimod will be administered to females of reproductive potential and the risks of exposure to etrasimod during pregnancy are unclear, DPMH recommends two PMRs: 1) a pregnancy exposure registry and 2) a complementary study of a different design, such as a claims database study (refer to the FDA draft Guidance for Industry *Postapproval Pregnancy Safety Studies*, published May 2019). DPMH recommends including language regarding the planned pregnancy exposure registry in subsection 8.1 and section 17 of labeling. The applicant's pharmacovigilance contact information needs to appear in subsection 8.1, but it is not required in section 17. After the pregnancy registry study protocol has been finalized, the applicant should submit a PAS to update PLLR labeling with the established pregnancy registry contact information.

Lactation

There are no data related to the presence of etrasimod in human milk, its effects on the breastfed infant, or its effects on milk production. Etrasimod was detected in the serum of the offspring of pregnant and lactating rats, and this information should be included the labeling for subsection 8.2. As no risks have been identified that would preclude breastfeeding, a risk/benefit statement about breastfeeding should be included in the labeling. A similar approach to labeling has been used with other S1P receptor modulators..

Because etrasimod will be administered to females of reproductive potential and the presence of etrasimod in human milk is unknown, DPMH recommends issuing a PMR for a milk-only lactation study. A mother-infant pair study may be required, depending on the results of the milk-only study.

Females and Males of Reproductive Potential

Clinical data do not suggest a drug-drug interaction between etrasimod and combined oral contraceptives. Nonclinical data do not indicate an adverse effect on male or female fertility. Given the potential fetal risks associated with etrasimod exposure during pregnancy, effective contraception is needed during treatment with etrasimod and for 7 days (30-hour half-life x 5-6 half-lives) after the last dose. The labeling should include this information in subsection 8.3.

The DPMH and DG teams discussed including pregnancy testing in labeling for etrasimod. Currently, Gilenya (fingolimod) is the only drug in the class that contains a pregnancy testing recommendation in subsection 8.3 due to concerns for potential teratogenicity seen in data from the Gilenya Pregnancy Registry.[32,33] Gilenya was the first drug in the class to be approved; therefore, there are more post-marketing data available for it than for other drugs in the class. Despite all drugs in the class having a Warning and Precaution for fetal risk in labeling due to animal study findings, the other drugs in the class (Mayzent – siponimod; Ponvory – ponesimod; Zeposia – ozanimod) do not currently include a pregnancy testing recommendation. To maintain consistency with other S1P receptor modulators for which adequate post-marketing data are not yet available, DPMH recommends not including a pregnancy testing recommendation in etrasimod labeling at this time. This could be updated in the future, depending on the post-marketing data.

LABELING RECOMMENDATIONS

DPMH recommended edits to the applicant's proposed labeling text in subsections 5.X, 8.1, 8.2, 8.3 and section 17 (see below). DPMH discussed our labeling recommendations with the Division on 5/1/2023. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling (Note: this labeling is based on the labeling for other approved S1P receptor modulators)

(b) (4)

[redacted]

[32] DPMH Review of Post-marketing Requirement (PMR) 1679-3 Pregnancy Registry Eighth Interim Report and Pregnancy Outcomes Intensive Monitoring (PRIM) Fifth Interim Report, Prior approval labeling supplement (PAS) #29 for Gilenya (fingolimod), NDA 22527, by Jane Liedtka, M.D., dated 12/9/2019. DARRTS Reference ID: 4528584.

[33] DPMH Maternal Health-Epidemiology Integrated Review of Post-marketing Requirement (PMR) 1679-3 Pregnancy Registry 11th Annual Interim Report and Pregnancy Outcomes Intensive Monitoring (PRIM) 8th Interim Report for Gilenya (fingolimod), NDA 22527, by Jane Liedtka, M.D. and Silvia Perez-Vilar, Ph.D., Pharm.D., dated 11/22/2022. DARRTS Reference ID: 5081845.

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

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/s/

KATHERINE G KRATZ
05/05/2023 12:58:35 PM

MIRIAM C DINATALE
05/05/2023 12:59:42 PM

LYNNE P YAO
05/09/2023 08:00:14 AM

enter for Drug Evaluation and Research
Division of Cardiology and Nephrology

CONSULT REVIEW

Application Type	NDA
Application Number(s)	216956
Priority or Standard	Standard
Submit Date(s)	10/14/22
Received Date(s)	10/18/22
PDUFA Goal Date	10/14/23
Division/Office	Division of Gastroenterology
Reviewer Name(s)	Rosalyn Adigun, MD, PharmD, Clinical Reviewer
Through	Mary Ross Southworth, PharmD, Deputy Division Director, Safety
	Norman Stockbridge, MD, PhD, Division Director
	Division of Cardiology and Nephrology (DCN)
To	Anum Shami, RPM, OND/ODEIII/DG
	Division of Gastroenterology
Established/Proper Name	Etrasimod
Mechanism of action	Selective sphingosine 1-phosphate receptor subtypes 1, 4, and 5 ($S1P_{1,4,5}$) modulator
Applicant	Arena Pharmaceuticals, Inc. (Arenas)
Dosage Form(s)	Tablet(s)
Applicant Proposed Dosing Regimen(s)	2 mg administered orally once daily
Applicant Proposed Indication(s)/Population(s)	Treatment of moderately to severely active ulcerative colitis (UC)
Reason for Consult	Division of Gastroenterology (DG) is requesting DCN's assistance with review of the cardiac safety data for Etrasimod under NDA 216856. Specifically, DG would like DCN's input on the following: 1. Please review the cardiac safety data that were submitted with this NDA in UC patients and comment on the acceptability of the proposed labeling (specifically, contraindications, warnings and precautions, and adverse reactions). Other drugs with similar mechanism include fingolimod, siponimod, ozanimod, and ponesimod. 2. Safety profile re: bradycardia and AV conduction delays 3. Need for titration or first-dose monitoring? 4. Risk of hypertension
Materials reviewed	Etrasimod.NDA.summary-clin-safety.pdf AdigunR.Etrasimod.clinical-overview.pdf AdigunR.annotated-draft-labeling-text. m1-6-2-meeting-background-materials.

Statement of Consult Request

Division of Gastroenterology (DG) has requested assistance from the Division of Cardiology and Nephrology (DCN) with review of the cardiac safety data for Etrasimod under NDA 216856. DCN has been asked to review and comment on the adequacy of the cardiac safety data submitted for the etrasimod development program, with respect to the following questions.

1. Please review the cardiac safety data that were submitted with this NDA in Ulcerative Colitis (UC) patients and comment on the acceptability of the proposed labeling (specifically, contraindications, warnings and precautions, and adverse reactions). Other drugs with similar mechanism include fingolimod, siponimod, ozanimod, and ponesimod.
2. Safety profile re: bradycardia and AV conduction delays
3. Need for titration or first-dose monitoring?
4. Risk of hypertension with Etrasimod

Executive summary

Arena Pharmaceuticals, Inc. is developing etrasimod, a selective sphingosine 1-phosphate receptor subtypes 1, 4, and 5 modulator ($S1P_{1,4,5}$) for the treatment of adult patients with moderate to severely active ulcerative colitis (UC).

1. The cardiac safety assessment to support the safety and tolerability of etrasimod for the treatment of patients with moderately to severely active UC was drawn primarily from the two pivotal UC studies (APD334-301 and APD334-302), and the phase 2 UC study (APD334-003) – collectively referred to as the Placebo-Controlled UC Pool. The cardiac safety information provided in the datasets and supplemented with supportive data from the earlier phase trials appear sufficient to support the proposed labeling.
2. Transient lowering of the heart rate and atrioventricular conduction delay was observed with the first dose administered and when therapy was reinitiated. These effects were self-limited and resolved within 8 hours without the need for intervention. The largest heart rate reduction was observed 3 hours after the first etrasimod dose -7.2 (8.98) bpm compared to 0.4 (7.93) bpm in the placebo group. Concomitant use of AV nodal blocking agents was not associated with an increase in events. HR did not drop below 40 bpm at any time point during the monitoring period.

3. A small but persistent increase in the SBP was observed in subjects exposed to etrasimod over the duration of the study. The largest mean change in SBP was observed at week 40 (mean increase 4 mmHg). The blood pressure trends observed with long-term etrasimod use appear similar to other S1P modulators (i.e., fingolimod) and this effect appears therapeutic class related. Blood pressure changes observed with long-term use in the pivotal studies should be described in the labeling. Blood pressure should be monitored with etrasimod use and managed according to local standards.
4. The Cardiovascular safety assessment submitted in the NDA provides adequate information to demonstrate an acceptable cardiac safety profile for etrasimod without the need for first-dose monitoring. However, DCN will work with DG to describe the cardiovascular effects of etrasimod on heart rate, AV conduction delays, and blood pressure. The labeling will align with other currently approved S1P receptor modulators. A REMS does not appear necessary for the safe use of etrasimod in moderate to severe Ulcerative Colitis.

Scientific Background

Sphingosine-1-phosphate [S1P] is a pleiotropic lipid mediator derived from the metabolism of membrane sphingolipids. S1P regulates lymphocyte migration, endothelial permeability, angiogenesis, cellular proliferation, cell migration, cell survival, apoptosis, stress fiber formation, and differentiation signaling. Treatment with S1P receptor modulators have been associated with transient lowering of the heart rate occurring approximately 3 hours after the initial dose, with attenuation of this effect seen on subsequent doses. This phenomenon is thought to be related to the effect of S1P receptors on the sinoatrial and atrioventricular nodes of the cardiovascular system. S1P1 agonism causes activation of G-protein coupled inwardly rectifying potassium (GIRK) channels that regulate cardiac pacemaker activity. Influx of potassium through GIRK channels has a negative chronotropic effect (i.e., reduced heart rate) and a negative dromotropic effect (i.e., reduced conduction speed) on the atrio-ventricular node. Etrasimod is therefore thought to reduce heart rate during the period between S1P1 activation and S1P1 internalization.

Once internalized, GIRK channels are no longer activated. Potassium inflow through the GIRK channels therefore decreases, thus attenuating the negative chronotropic and negative dromotropic effects.

The transient bradyarrhythmic and atrioventricular (AV) conduction delay effects of S1P receptor modulators are identified risks that have been described in the labeling for other approved S1P modulators (fingolimod, siponimod, and ozanimod) with mitigation strategies adopted to assure safe use. The Warnings and Precautions section of the fingolimod and siponimod labeling describes transient AV conduction delays and first dose transient reduction in heart rate which are generally asymptomatic and require first dose monitoring for 6 hours upon initiation of therapy or with reinitiation following therapy discontinuation for more than 4 (siponimod) or14 (fingolimod) days. If symptoms occur after the first dose or with therapy reinitiation, continuous monitoring is required until symptom resolution.

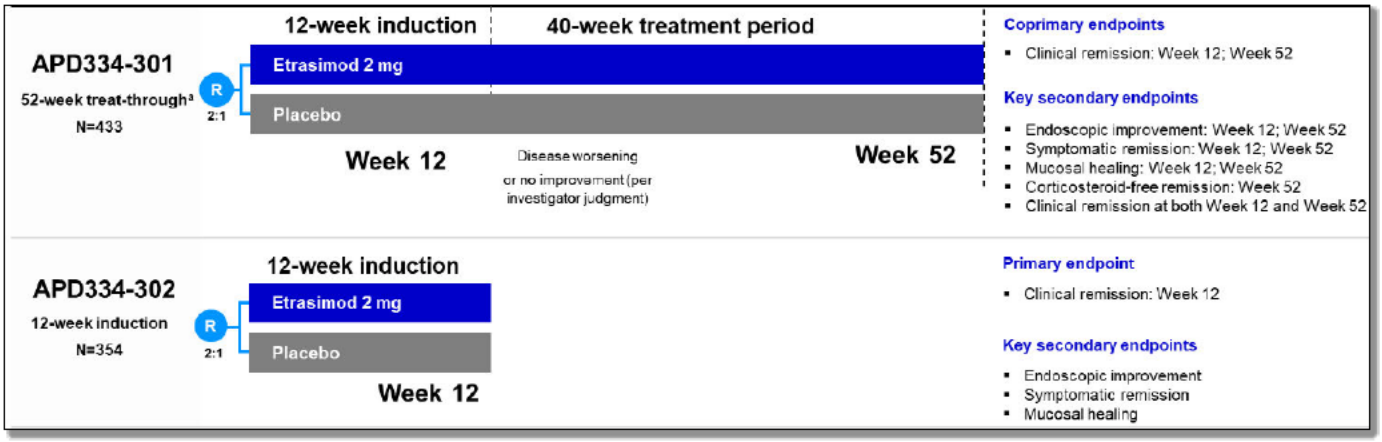
Other class effects with S1P receptor modulators involve blood pressure regulation. These effects have been associated with the effects on the $S1PR_1$ and $S1PR_3$ receptor subtypes. The effects on blood pressure have been attributed to functional antagonism of $S1PR_1$ resulting in mild increases in systolic and diastolic blood pressure associated with long-term (over 8 weeks) use. However, a few cases of posterior reversible encephalopathy have also been associated with exposure to this drug class.

At the time of approval of the first-in-class S1P receptor modulator in 2010, the Sponsor proposed a Risk Evaluation and Mitigation Strategy (REMS) to educate prescribers and patients about the potential serious risks of fingolimod. CV risks highlighted included bradycardia/bradyarrhythmia events. The REMS included a medication guide and communication plan. Additional safety concerns were also addressed in the warnings and precautions sections of the label. A REMS modification approved in 2012 eliminated the Medication Guide as an element of the REMS. A similar precedence was followed during the approval of siponimod. However, when ozanimod was approved in 2020, it was determined that based on the cumulative experience with other S1P modulators and available data, a REMS was not necessary to ensure safe use.

SECTION II –REVIEW OF SUBMITTED MEETING BACKGROUND MATERIALS

Two phase 3 studies (APD334-301 and APD334-302) and a phase 2 study (APD334-003) provide the substantive evidence of efficacy to support the indication of Etrasimod for the treatment of moderate to severely active UC at the recommended dose of 2 mg once daily. Studies APD334-301 (etrasimod N = 289, placebo N = 144) and APD334-302 (etrasimod N = 238, placebo N = 116) were global multicenter, randomized, double-blind, placebo-controlled studies with subjects randomized 2:1 to receive etrasimod 2 mg or placebo once daily for 12 weeks (APD334-302) or up to 52 weeks (APD334-301). Study APD334-003 (Etrasimod 1 mg N = 52 subjects, Etrasimod 2 mg N = 50, and placebo N= 54) was a 12-week randomized, double blind, placebo controlled parallel group dose-ranging study of etrasimod 1 mg and 2 mg compared to placebo.

Figure 1: Study Design for the pivotal phase 3 UC studies



The cardiac safety assessment to support the safety and tolerability of etrasimod for the treatment of patients with moderately to severely active UC was drawn primarily from the two pivotal UC studies (APD334-301 and APD334-302), and the phase 2 UC study (APD334-003) – collectively referred to as the Placebo-Controlled UC Pool.

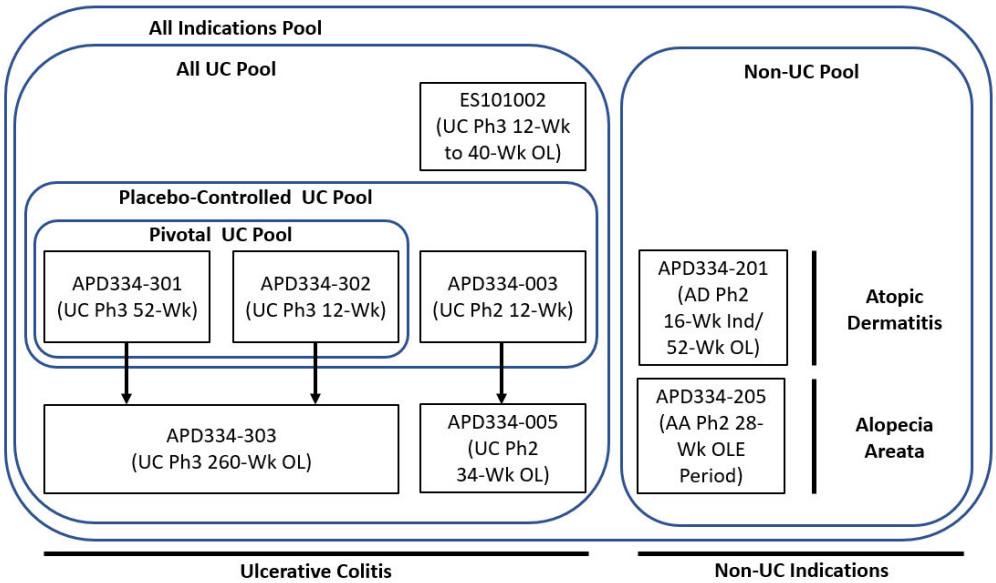
The pivotal studies excluded patients at high risk for an arrhythmic event, recently diagnosed or treated for conditions that affect cardiovascular function. Key exclusion criteria included history

of secondary degree of higher AV blocks, sinus node dysfunction, recurrent symptomatic bradyarrhythmic events, myocardial infarction, unstable angina, stroke or transient ischemic attack, decompensated heart failure requiring hospitalization or Class III/IV heart failure within 6 months of the screening period. Patients undergoing treatment with anti-arrhythmic drugs were also excluded.

The median age of subjects in the Placebo-Controlled UC Pool was 38 -years (IQR, 17 to 78). At baseline, the disease severity scores were similar between the 3 studies that comprise the Placebo-Controlled UC Pool. Concomitant AV nodal blocking agents use was higher in the etrasimod arm compared to placebo, however the relative difference between both groups was less than 2% except for beta-blocker use (6% in etrasimod arm versus 3.8% in placebo arm). Underlying cardiac disorders were higher in the etrasimod arm compared to placebo. (Appendix 1).

Additional data on the CV safety profile of etrasimod beyond 52-weeks was derived from the UC Pool which included the Placebo-controlled UC Pool and the open label extension studies (APD 334-303, APD 334-005, and ES101003).

Fig. 2: Pooling Strategy for Integrated Analyses of Safety



Note: Subjects in Study APD334-303 may enroll from parent studies not represented in this figure. Source: Adapted from ISS SAP,

Ind, induction; OL, open label; Ph2, Phase 2; Ph3, Phase 3; Wk, week.

In the Placebo controlled UC Pool, the mean exposure to the investigational drug was longer in the etrasimod 2 mg group (25.02 weeks) compared to the etrasimod < 2 mg (11.45 weeks) and placebo (19.12 weeks) groups. The most frequently reported (≥ 2% of subjects in any treatment group) reasons for treatment discontinuation were progressive disease, withdrawal by subject, and adverse events.

The Cardiac TEAEs by preferred term (PT) occurring in ≥ 1% of subjects in the etrasimod 2 mg group and occurring more frequently (by ≥ 1% point) in the etrasimod 2 mg group compared to placebo were Hypertension (2.1% vs.1.0%), and Bradycardia (1% vs.0 %) in the etrasimod 2 mg and placebo respectively. Cardiac TEAE PTs leading to permanent study treatment discontinuation in ≥ 2 subjects in any treatment group were bradyarrhythmia, and sinus bradycardia. No subjects had Grade 5 (fatal) TEAEs in any treatment group.
The Sponsor also conducted a retrospective medical review to identify Sponsor-Designated Events of Interest (SDEI) based on the mechanism of action of etrasimod, prior experience with other agents acting via a similar mechanism, and disease-specific clinical judgment. The retrospective review was blinded for the pivotal studies in UC and all ongoing studies (all indications). Prespecified Cardiovascular SDEI include bradycardia, atrioventricular (AV) conduction delays, and hypertension. In the Pivotal UC and All Indications Pool, all subjects with SDEI in the bradycardia and AV conduction delay subcategories were in the etrasimod 2 mg group. However, these patients did not experience hemodynamic instability or clinical events.

The **Pivotal UC Pool** which included the 12-week and 52- week phase 3 studies was the primary pool analyzed for the first dose effect on heart rate observed with etrasimod. The results of the CV safety assessment are described below.

- There were no significant differences in the baseline heart rate in both groups prior to etrasimod exposure. The baseline (pre-dose) heart rate was 74.1(10.9) bpm in the etrasimod arm compared to 75.5 (10.2) bpm in the placebo arm.

- The greatest mean (SD) heart rate reduction was observed 3 hours after the first dose and corresponded to a mean (SD) change of -7.2 (8.98) bpm in the etrasimod 2 mg group compared to 0.4 (7.93) bpm in the placebo arm
- Day 1 changes in HR in the etrasimod 2 mg group were similar for subjects on concomitant antiarrhythmics or AV nodal agents compared to subjects not currently being treated with these agents
- While the proportion of subjects with an HR nadir < 55 bpm on Day 1 was greater in the etrasimod 2 mg group compared to the placebo group (etrasimod 2 mg: 98 subjects, 18.6%; placebo: 9 subjects, 3.5%), the nadir HR did not drop below 40 bpm at any time point during the monitoring period.
- 13 (2.5%) subjects in the etrasimod 2 mg group had a post-baseline HR measurement <50 bpm on Day 1, however no events of clinical consequence (e.g., syncope or loss of consciousness) or clinically significant decreases in BP were reported and no pharmacologic intervention was required.
- 13 subjects met study criteria for extended monitoring on Day 2 (none in the placebo arm). The mean pre-dose HR 58.8 (8.99) bpm in this group was lower than baseline (pre-dose 1). However, the heart rate reduction after the second dose was less (mean reduction at 3 hours post dose -2.6 (4.06) bpm) compared to placebo.
- The effects of etrasimod 2 mg on HR following treatment re-initiation in the Pivotal UC Pool was similar but lower in magnitude compared to the HR effects observed on Day 1. After reinitiation of etrasimod, mean time to minimum heart rate was 2.66 (1.09) hours and only 1 patient has a heart rate below 64 bpm (55-59 bpm). *(etrasimod 2 mg: 9 subjects; placebo: no subjects).*

Summary of ECG changes (Specifically atrioventricular conduction delays)

- There were no significant differences on the presence of a first-degree atrioventricular block (defined as a PR interval >200 ms) on baseline ECG between the Etrasimod (22/521) and Placebo arms (12/257).

- There was one subject with a second-degree AV block (Mobitz type 1) in the placebo arm at baseline
- There were no subjects with a second-degree AV block, Mobitz type 2 or higher at baseline
- On Day 1 ECG screening (post dose), there were 38/510 (7.5%) versus 8/251 (3.2) subjects with a first-degree AV block in the etrasimod versus placebo arms
- At week 52, there were similar rates of first-degree AV block in etrasimod and placebo arm of the Pivotal UC Pool safety database.

Reviewer's comments: Bradycardia (symptomatic and asymptomatic), first-degree atrioventricular block, and second-degree atrioventricular block (Mobitz Type I) occurred more frequency in the etrasimod 2 mg group compared to placebo. These effects were transient and resolved within 8 hours in most cases. In the few instances that this was accompanied with symptoms, the patients had other comorbid conditions or exposure to pharmacotherapy that could have predisposed them to these effects (i.e., hypothyroidism, underlying cardiac conduction abnormalities). Description of these events in etrasimod labeling to increase provider vigilance in patients with underlying conduction abnormalities, comorbid conditions, and intercurrent illness would be an effective strategy in mitigating bradyarrhythmic events associated with the first dose of etrasimod.

The use of AV-nodal blocking agents or anti-arrhythmic agents was higher in the etrasimod group compared to placebo. However, the presence of these agents did not appear to predispose patients to the negative chronotropic or dromotropic effects seen with the first dose effect. However, the total numbers of subjects on these medications were small and the generalization of the observed effects is limited. (Appendix 1)

Effects of Etrasimod on Blood Pressure

Increase in BP is a described class effect associated with long-term use of S1P receptor modulators. The BP effects have been described in studies of S1P receptor modulators in patients with Multiple Sclerosis (MS) where increases in both systolic and diastolic BP of 1 to 4 mmHg with fingolimod and Siponimod treatment relative to placebo were observed. While the mechanism of this effect remains incompletely explained, the associated increase in blood pressure is typically seen with long-term use.

In the etrasimod clinical development program, the sponsor designated hypertension as a Sponsor designated event of interest (SDEI) if one or more of the following criteria were met:

- Sustained systolic BP elevation was ≥ 160 mmHg
- Sustained diastolic BP elevation was ≥ 100 mmHg
- Medication was added for BP control

Blood pressure was measured manually or by automated device during the pivotal study. Subjects' arms were exposed and supported at heart level and an appropriately sized cuff (cuff bladder encircling at least 80% of the arm) was used. Measurements were obtained with the subject in the seated position with legs uncrossed.

In the Pivotal UC Pool, 13 subjects (2.5%, EAIR 0.05) in the etrasimod 2 mg group and 2 subjects (0.8%, EAIR 0.02) in the placebo group had an SDEI in the hypertension subcategory.

First dose Change in Blood Pressure

The pivotal UC pool was also the primary pool use to characterize the impact of the first etrasimod dose on changes in blood pressure.

- There were no significant differences in the baseline (pre-dose) systolic and diastolic blood pressure readings between the etrasimod and placebo arms
  - Systolic blood pressure (SBP) 120.7 (12.51) mmHg versus 121.3 (13.08) mmHg in the etrasimod and placebo arms respectively
  - Diastolic blood pressure (DBP) 75.8 (8.54) mmHg versus 77.2 (9.56) mmHg in the etrasimod and placebo arms respectively
- The number of subjects with a medical history of "hypertension/essential hypertension/hypertensive angiopathy/ white coat hypertension was balanced between both arms of the study with 79/527 (14.9%) versus 41/260 (15.7%) in the etrasimod versus placebo groups respectively
- During the in-clinic 4-hour monitoring period, the mean change from baseline in SBP ranged from -0.5 to -2.2 mmHg in the etrasimod 2 mg group (compared to -0.6 to

-2.1 mmHg in the placebo group). The largest mean change from baseline in systolic BP occurred at 2-hour post dose

- During the in-clinic 4-hour monitoring period, the mean change from baseline in DBP ranged from -2.5 to -3.9 mmHg in the etrasimod 2 mg group (compared to -0.5 to -1.6 mmHg in the placebo group). The largest mean change from baseline occurred at Hour 2
- No potential dose-dependent effects of etrasimod on systolic or diastolic BP were observed on Day 1

Change in Blood Pressure Over Time

- For the etrasimod development program, markedly abnormal BP values were defined as systolic BP values ≤ 90, > 160, or > 180 mmHg or diastolic BP values ≤ 50, > 100, and >120 mmHg occurring any time post-baseline.

- Increases in systolic BP compared to baseline were observed starting at Week 2 and persisted during the study with a mean change from baseline to week 52 of 2.2 (11.08) mmHg in the etrasimod group compared to the placebo arm -1.3 (9.16) mmHg.

- The maximum mean (SD) change in SBP compared to baseline was 3.6 (11.59) mmHg at Week 40, compared to a 1.4 (10.64) mmHg increase in the placebo-treated subjects at Week 40

- There were no clinically meaningful changes in diastolic BP over time in either group with changes in diastolic BP of approximately 1 to 2 mmHg in the etrasimod group compared to < 1 mmHg in the placebo group

Reviewer's comments: A small but persistent increase in the SBP can be appreciated in the subjects exposed to etrasimod over the duration of the study. The largest mean change in SBP was observed at week 40 and by week 52, this change while still present is lower. Based on similar observations described in other S1P modulators (i.e., fingolimod) this association appears drug-related. However, the mechanism is unknown. Blood pressure changes observed in the pivotal studies should be described in the labeling. Based on the observed class effect on blood pressure with long-term use, it is recommended that BP should be monitored during treatment with etrasimod and managed according to local standards.

Labeling

DCN will work with DG to describe the cardiovascular effects of etrasimod on heart rate, AV conduction delays, and blood pressure. The labeling will align with other currently approved S1P receptor modulators. A REMS does not appear necessary for the safe use of etrasimod in moderate to severe Ulcerative Colitis.

Table 2. Systolic and Diastolic Blood Pressure and Change from Predose -(Pivotal UC Pool)

	Etrasimod 2 mg (N=527)	Placebo (N=260)
Systolic Blood Pressure (mmHg)		
Pre-dose		
Mean (SD)	120.7 (12.51)	121.3 (13.08)
Median (Min, Max)	120.0 (90, 158)	120.0 (90, 174)
Change from Pre-dose Post-dose		
1-hour Post-dose	N=524	N=260
Mean (SD)	-1.4 (9.19)	-2.1 (8.92)
Median (Min, Max)	-1.0 (-42, 28)	-1.0 (-32, 22)
2-hour Post-dose	N=525	N=258
Mean (SD)	-2.2 (10.00)	-0.6 (9.79)
Median (Min, Max)	1.0 (-38, 31)	0.0 (-40, 34)
3 Hours Post-dose	N=525	N=258
Mean (SD)	-1.7 (9.92)	-1.6 (10.15)
Median (Min, Max)	-1.0 (-35, 35)	-1.0 (-44, 47)
4 Hours Post-dose		
Mean (SD)	-0.5 (9.23)	-0.7 (8.76)
Median (Min, Max)	0.0 (-30, 31)	0.0 (-26, 32)
Diastolic Blood Pressure (mmHg)		
Pre-dose	N=526	N=260
Mean (SD)	75.8 (8.54)	77.2 (9.56)
Median (Min, Max)	75.0 (55, 109)	77.0 (57, 119)
Change from Pre-dose Post-dose		
1-hour Post-dose	N=524	N=260
Mean (SD)	-2.5 (7.03)	-1.5 (6.66)
Median (Min, Max)	-2.0 (-29, 22)	0.0 (-30, 28)
2-hour Post-dose	N=525	N=258
Mean (SD)	-3.9 (8.04)	-1.4 (7.62)
Median (Min, Max)	3.0 (-32, 28)	-1.0 (-33, 25)
3 Hours Post-dose	N=525	N=258
Mean (SD)	-3.4 (7.99)	-1.6 (7.32)
Median (Min, Max)	-3.0 (-43, 28)	-1.0 (-32, 20)
4 Hours Post-dose		
Mean (SD)	-2.7 (7.28)	-0.5 (7.13)
Median (Min, Max)	-2.0 (-30, 35)	0.0 (-30, 23)

Baseline is defined, by study treatment group received, as the last non missing measurement taken on or prior to the study treatment group start date.
Source: ISS Table 14.3.14.1.1

Table 3.Incidence of Vital Signs Markedly Abnormal Values by Study Visit (Pivotal UC Pool)

Parameter Analysis Visit Markedly Abnormal Criterion	Etrasimod 2 mg/day (N=527) n (%)	Placebo (N=260) n (%)
Systolic Blood Pressure (mmHg)		
Baseline	527	260
<= 90	5 (0.9)	2 (0.8)
> 160	0	2 (0.8)
Week 2	511	249
<= 90	0	1 (0.4)
> 160	0	0
> 180	0	0
Week 4	503	246
<= 90	3 (0.6)	2 (0.8)
> 160	4 (0.8)	0
> 180	0	0
Week 8	494	244
<= 90	2 (0.4)	1 (0.4)
> 160	3 (0.6)	0
> 180	0	0
Week 12	474	231
<= 90	1 (0.2)	1 (0.4)
> 160	3 (0.6)	1 (0.4)
> 180	1 (0.2)	0
Week 16	206	73
<= 90	1 (0.5)	1 (1.4)
> 160	2 (1.0)	0
> 180	0	0
Week 20	193	61
<= 90	1 (0.5)	0
> 160	1 (0.5)	0
> 180	0	0
Week 24	190	59
<= 90	0	0
> 160	2 (1.1)	0
> 180	0	0
Week 32	182	54
<= 90	2 (1.1)	0
> 160	1 (0.5)	0
> 180	0	0

APPENDIX

Appendix 1

Pivotal UC Pool concomitant medications

Beta-blocker (BB) use in the Etrasimod arm 32/527 (6%) vs. Placebo 10/260(3.8%)
Calcium Channel blocker (CCB) in Etrasimod arm 26/527 (4.9%) vs. Placebo 9/260 (3.5%)
Antiarrhythmic agents in Etrasimod arm (3/260) versus 1/260
Underlying cardiac disorders 36/527 (6.8%) versus placebo 9/260 (3.5%) AVB 1 and 2

Placebo controlled UC Pool concomitant medications

BB: Etrasimod 2 mg 33/577 (5.7%) vs. Etrasimod < 2 mg 3/52 (5.8%) vs. Placebo 13/314 (4.1%)
CCB: Etrasimod 2 mg 27/577 (4.7%) vs. Etrasimod < 2 mg 1/52(1.9%) vs. Placebo 11/314(3.5%)
Antiarrhythmic agents in Etrasimod 2 mg (1/577) versus placebo 0/314
Cardiac disorders 38/577 in Etrasimod 2 mg (6.6%) vs. Etrasimod 1 mg 5/52 (9.6%) vs placebo 13/314 (4.1%) – Placebo has AVB 1 and 2

Appendix 2: Summary of Cardiac Effects on Vital Signs on Day 1 (Pivotal UC Pool)

	Result in Pivotal UC Pool	
Parameter Measured on Day 1	**Etrasimod 2 mg**	**Placebo**
Time to Day 1 nadir HR following dose (hours)		
n	526	260
Mean (SD)	2.49 (1.113)	2.18 (1.137)
Median (Min, Max)	2.08 (0.8, 9.9)	2.00 (0.8, 4.3)
Nominal hourly postdose timepoint with minimum heart rate observed, n (%)		
Hour 1	107 (20.3)	100 (38.5)
Hour 2	178 (33.8)	54 (20.8)
Hour 3	118 (22.4)	59 (22.7)
Hour 4	121 (23.0)	47 (18.1)
Incidence of subject's Day 1 nadir on Day 1 (n [%])[a]		
≥ 65 bpm	223 (42.3)	199 (76.5)
60 to 64 bpm	131 (24.9)	35 (13.5)
55 to 59 bpm	75 (14.2)	17 (6.5)
50 to 54 bpm	85 (16.1)	9 (3.5)
45 to 49 bpm	9 (1.7)	0
40 to 44 bpm	4 (0.8)	0
< 40 bpm	0	0
Subjects not meeting discharge criteria at Hour 4 postdose on Day 1 as determined by Investigator (n [%])	21 (4.0)	1 (0.4)
Heart Rate (beats/min) Incidence of Vital Signs Markedly Abnormal Values on Day 1 by Postdose Timepoint, n (%)		
Predose	526	260
< 40	0	0
< 50	0	0
>100	5 (1.0)	4 (1.5)
1 Hour Postdose	525	260
< 50 and decrease from predose of > 10[b]	3 (0.6)	0
< 40	0	0
< 50	3 (0.6)	0
>100	2 (0.4)	5 (1.9)
2 Hours Postdose	525	258
< 50 and decrease from predose of > 10[b]	5 (1.0)	0
< 40	0	0

Summary of Cardiac Effects on Vital Signs on Day 1 (Pivotal UC Pool) (Cont'd)

	Result in Pivotal UC Pool	
Parameter Measured on Day 1	**Etrasimod 2 mg**	**Placebo**
< 50	5 (1.0)	0
>100	1 (0.2)	6 (2.3)
3 Hours Postdose	524	258
< 50 and decrease from predose of > 10[b]	5 (1.0)	0
< 40	0	0
< 50	7 (1.3)	0
>100	3 (0.6)	7 (2.7)
4 Hours Postdose	526	259
< 50 and decrease from predose of > 10[b]	2 (0.4)	0
< 40	0	0
< 50	3 (0.6)	0
>100	1 (0.2)	1 (0.4)

[a] If minimum heart rate is attained at multiple postdose timepoints, only the earliest timepoint is counted.
[b] < 50 bpm and decrease from predose (Baseline) of > 10 bpm postdose on Day 1.
Percentages are based on the number of subjects in the pool unless specified otherwise.
Source: ISS Tables 14.3.14.1.1, 14.3.14.3.1, 14.3.14.4.1, 14.3.1.5.1, and 14.3.14.6.1

Appendix 3. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term- Pivotal UC Pool

System Organ Class Preferred Term	Etrasimod 2 mg/day (N=527) n (%) [EAIR]	Placebo (N=260) n (%) [EAIR]
Cardiac disorders	21 (4.0) [0.08]	4 (1.5) [0.04]
Bradycardia	5 (0.9) [0.02]	0
Sinus bradycardia	4 (0.8) [0.01]	0
Tachycardia	4 (0.8) [0.01]	3 (1.2) [0.03]
AV-Block (First degree)	2 (0.4) [<0.01]	0
Palpitations	2 (0.4) [<0.01]	1 (0.4) [<0.01]
Atrial Fibrillation	1 (0.2) [<0.01]	0
AV-Block (Second degree)	1 (0.2) [<0.01]	0
Chronic failure cardiac	1 (0.2) [<0.01]	0
Coronary artery disease	1 (0.2) [<0.01]	0
Sinus arrhythmia	1 (0.2) [<0.01]	0
Sinus tachycardia	1 (0.2) [<0.01]	0
Ventricular extrasystoles	1 (0.2) [<0.01]	0

Appendix 4. Treatment-Emergent Sponsor-Designated Events of Interest by Category, Subcategory, and Preferred Term - Pivotal UC Pool

Category Subcategory Preferred Term	Etrasimod 2 mg/day (N=527) n (%) [EAIR]	Placebo (N=260) n (%) [EAIR]
Subjects with at least One TESDEI	39 (7.4) [0.15]	14 (5.4) [0.14]
Cardiovascular Events	20 (3.8) [0.07]	2 (0.8) [0.02]
Hypertension	13 (2.5) [0.05]	2 (0.8) [0.02]
Hypertension	11 (2.1) [0.04]	1 (0.4) [<0.01]
Blood pressure increased	1 (0.2) [<0.01]	0
Hypertensive crisis	1 (0.2) [<0.01]	0
Essential hypertension	0	1 (0.4) [<0.01]
Bradycardia	4 (0.8) [0.01]	0
Bradycardia	2 (0.4) [<0.01]	0
Sinus bradycardia	2 (0.4) [<0.01]	0
AV conduction delay	3 (0.6) [0.01]	0
Atrioventricular block first degree	2 (0.4) [<0.01]	0
Atrioventricular block second degree	1 (0.2) [<0.01]	0

Appendix 5. Treatment-Emergent Sponsor-Designated Events of Interest in Cardiovascular Events by Category, Subcategory, Preferred Term, and Day of Onset Pivotal UC Pool

Treatment-Emergent Sponsor-Designated Events of Interest in Cardiovascular Events by Category, Subcategory, Preferred Term, and Day of Onset
Pivotal UC Pool

Day of Onset Category Subcategory Preferred Term	Etrasimod 2 mg/day (N=527) n (%) [EAIR]	Placebo (N=260) n (%) [EAIR]
On Day 1		
Subjects with at least One TESDEI	6 (1.1) [0.02]	0
Cardiovascular Events	6 (1.1) [0.02]	0
AV conduction delay	3 (0.6) [0.01]	0
Atrioventricular block first degree	2 (0.4) [<0.01]	0
Atrioventricular block second degree	1 (0.2) [<0.01]	0
Bradycardia	3 (0.6) [0.01]	0
Sinus bradycardia	2 (0.4) [<0.01]	0
Bradycardia	1 (0.2) [<0.01]	0

Appendix 6. Treatment-Emergent Sponsor-Designated Events of Interest in Cardiovascular Events by Category, Subcategory, Preferred Term, and Day of Onset - Pivotal UC Pool

Treatment-Emergent Sponsor-Designated Events of Interest in Cardiovascular Events by Category, Subcategory, Preferred Term, and Day of Onset
Pivotal UC Pool

Day of Onset Category Subcategory Preferred Term	Etrasimod 2 mg/day (N=527) n (%) [EAIR]	Placebo (N=260) n (%) [EAIR]
After Day 1		
Subjects with at least One TESDEI	15 (2.8) [0.06]	2 (0.8) [0.02]
Cardiovascular Events	15 (2.8) [0.06]	2 (0.8) [0.02]
Hypertension	13 (2.5) [0.05]	2 (0.8) [0.02]
Hypertension	11 (2.1) [0.04]	1 (0.4) [<0.01]
Blood pressure increased	1 (0.2) [<0.01]	0
Hypertensive crisis	1 (0.2) [<0.01]	0
Essential hypertension	0	1 (0.4) [<0.01]
Bradycardia	2 (0.4) [<0.01]	0
Bradycardia	2 (0.4) [<0.01]	0

Appendix 7. Cardiac Treatment-Emergent Adverse Events on Day 1 by Preferred Term Pivotal UC Pool

Preferred Term	Etrasimod 2 mg/day (N=527) n (%) [EAIR]	Placebo (N=260) n (%) [EAIR]
Subject with at Least One Cardiac TEAE	11 (2.1) [0.04]	1 (0.4) [<0.01]
Bradycardia	4 (0.8) [0.01]	0
Sinus bradycardia	4 (0.8) [0.01]	0
Atrioventricular block first degree	2 (0.4) [<0.01]	0
Atrioventricular block second degree	1 (0.2) [<0.01]	0
Sinus arrhythmia	1 (0.2) [<0.01]	0
Tachycardia	0	1 (0.4) [<0.01]

Appendix 8. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Placebo-Controlled UC Pool

System Organ Class Preferred Term	Etrasimod 2 mg/day (N=577) n (%) [EAIR]	Etrasimod < 2 mg/day (N=52) n (%) [EAIR]	Etrasimod Any Dose (N=629) n (%) [EAIR]	Placebo (N=314) n (%) [EAIR]
Cardiac disorders	24 (4.2) [0.09]	1 (1.9) [0.08]	25 (4.0) [0.09]	4 (1.3) [0.03]
Bradycardia	6 (1.0) [0.02]	0	6 (1.0) [0.02]	0
Sinus bradycardia	5 (0.9) [0.02]	0	5 (0.8) [0.02]	0
Tachycardia	4 (0.7) [0.01]	0	4 (0.6) [0.01]	3 (1.0) [0.03]
Atrioventricular block first degree	2 (0.3) [<0.01]	0	2 (0.3) [<0.01]	0
Atrioventricular block second degree	2 (0.3) [<0.01]	0	2 (0.3) [<0.01]	0
Palpitations	2 (0.3) [<0.01]	1 (1.9) [0.08]	3 (0.5) [0.01]	1 (0.3) [<0.01]
Ventricular extrasystoles	2 (0.3) [<0.01]	0	2 (0.3) [<0.01]	0
Atrial fibrillation	1 (0.2) [<0.01]	0	1 (0.2) [<0.01]	0
Cardiac failure chronic	1 (0.2) [<0.01]	0	1 (0.2) [<0.01]	0
Coronary artery disease	1 (0.2) [<0.01]	0	1 (0.2) [<0.01]	0
Sinus arrhythmia	1 (0.2) [<0.01]	0	1 (0.2) [<0.01]	0
Sinus tachycardia	1 (0.2) [<0.01]	0	1 (0.2) [<0.01]	0

Appendix 9. Treatment-Emergent Sponsor-Designated Events of Interest by Category, Subcategory, and Preferred Term - All Indications Pool

Category Subcategory Preferred Term	Etrasimod 2 mg/day (N=1077) n (%) [EAIR]	Etrasimod < 2 mg/day (N=99) n (%) [EAIR]	Etrasimod > 2 mg/day (N=18) n (%) [EAIR]	Etrasimod Any Dose (N=1107) n (%) [EAIR]	Placebo (N=368) n (%) [EAIR]
Subjects with at least One TESDEI	77 (7.1) [0.09]	3 (3.0) [0.12]	0	80 (7.2) [0.09]	19 (5.2) [0.14]
Cardiovascular Events	33 (3.1) [0.04]	1 (1.0) [0.04]	0	34 (3.1) [0.04]	3 (0.8) [0.02]
Hypertension	19 (1.8) [0.02]	1 (1.0) [0.04]	0	20 (1.8) [0.02]	3 (0.8) [0.02]
Hypertension	17 (1.6) [0.02]	1 (1.0) [0.04]	0	18 (1.6) [0.02]	2 (0.5) [0.01]
Blood pressure increased	1 (<0.1) [<0.01]	0	0	1 (<0.1) [<0.01]	0
Hypertensive crisis	1 (<0.1) [<0.01]	0	0	1 (<0.1) [<0.01]	0
Essential hypertension	0	0	0	0	1 (0.3) [<0.01]
AV conduction delay	8 (0.7) [<0.01]	0	0	8 (0.7) [<0.01]	0
Atrioventricular block first degree	4 (0.4) [<0.01]	0	0	4 (0.4) [<0.01]	0
Atrioventricular block second degree	4 (0.4) [<0.01]	0	0	4 (0.4) [<0.01]	0
Bradycardia	7 (0.6) [<0.01]	0	0	7 (0.6) [<0.01]	0
Bradycardia	4 (0.4) [<0.01]	0	0	4 (0.4) [<0.01]	0
Sinus bradycardia	3 (0.3) [<0.01]	0	0	3 (0.3) [<0.01]	0
AV conduction delay / Bradycardia	1 (<0.1) [<0.01]	0	0	1 (<0.1) [<0.01]	0
Arrhythmia	1 (<0.1) [<0.01]	0	0	1 (<0.1) [<0.01]	0

Appendix 10. Cardiac Treatment-Emergent Adverse Events on Day 1 by Preferred Term Placebo-Controlled UC Pool

Preferred Term	Etrasimod 2 mg/day (N=577) n (%) [EAIR]	Etrasimod < 2 mg/day (N=52) n (%) [EAIR]	Etrasimod Any Dose (N=629) n (%) [EAIR]	Placebo (N=314) n (%) [EAIR]
Subject with at Least One Cardiac TEAE	14 (2.4) [0.05]	0	14 (2.2) [0.05]	1 (0.3) [<0.01]
Bradycardia	5 (0.9) [0.02]	0	5 (0.8) [0.02]	0
Sinus bradycardia	5 (0.9) [0.02]	0	5 (0.8) [0.02]	0
Atrioventricular block first degree	2 (0.3) [<0.01]	0	2 (0.3) [<0.01]	0
Atrioventricular block second degree	2 (0.3) [<0.01]	0	2 (0.3) [<0.01]	0
Sinus arrhythmia	1 (0.2) [<0.01]	0	1 (0.2) [<0.01]	0
Ventricular extrasystoles	1 (0.2) [<0.01]	0	1 (0.2) [<0.01]	0
Tachycardia	0	0	0	1 (0.3) [<0.01]

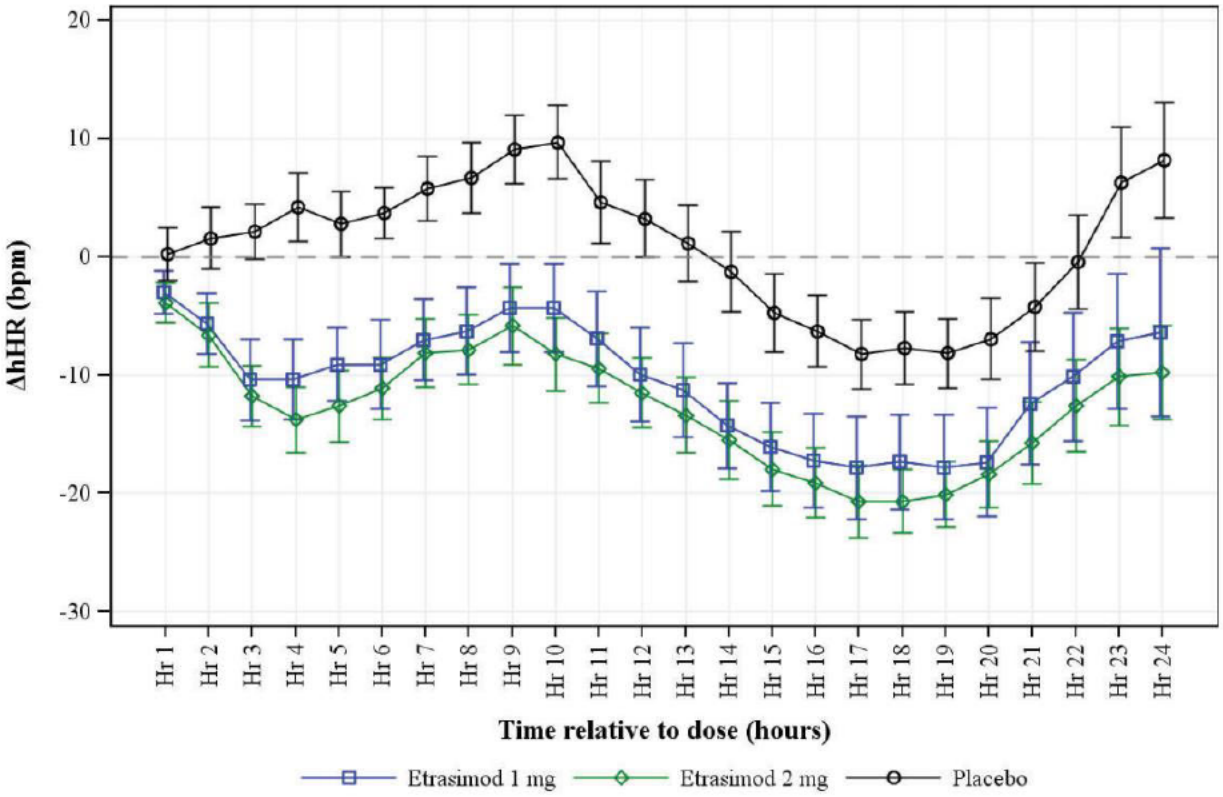
Appendix 11. Cardiac Treatment-Emergent Adverse Events on Day 1 by Preferred Term All UC Pool

Preferred Term	Etrasimod 2 mg/day (N=942) n (%) [EAIR]	Etrasimod < 2 mg/day (N=52) n (%) [EAIR]	Etrasimod Any Dose (N=956) n (%) [EAIR]	Placebo (N=322) n (%) [EAIR]
Subject with at Least One Cardiac TEAE	21 (2.2) [0.03]	0	21 (2.2) [0.03]	1 (0.3) [<0.01]
Bradycardia	7 (0.7) [<0.01]	0	7 (0.7) [<0.01]	0
Sinus bradycardia	6 (0.6) [<0.01]	0	6 (0.6) [<0.01]	0
Atrioventricular block first degree	4 (0.4) [<0.01]	0	4 (0.4) [<0.01]	0
Atrioventricular block second degree	3 (0.3) [<0.01]	0	3 (0.3) [<0.01]	0
Ventricular extrasystoles	2 (0.2) [<0.01]	0	2 (0.2) [<0.01]	0
Sinus arrhythmia	1 (0.1) [<0.01]	0	1 (0.1) [<0.01]	0
Tachycardia	0	0	0	1 (0.3) [<0.01]

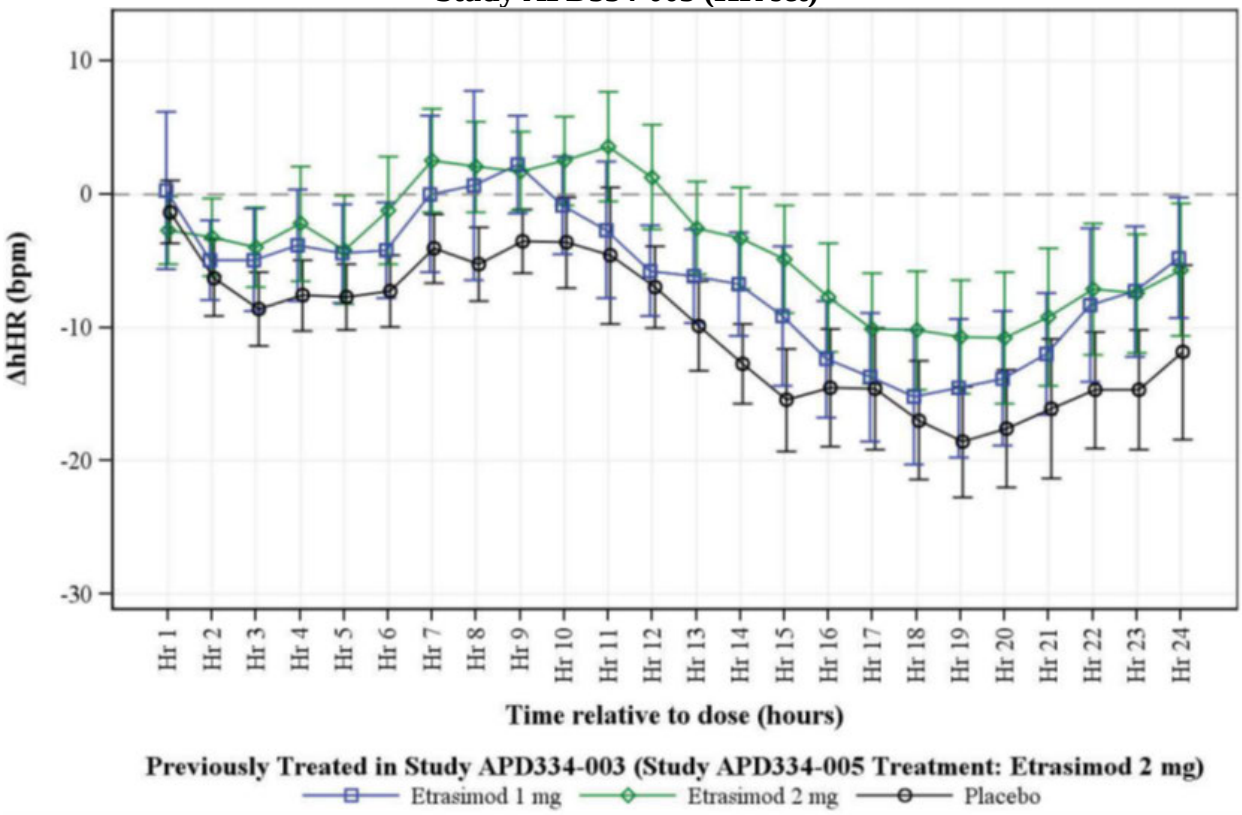
Appendix 12. Cardiac Treatment-Emergent Adverse Events on Day 1 by Preferred Term
All Indications Pool

Preferred Term	Etrasimod 2 mg/day (N=1077) n (%) [EAIR]	Etrasimod < 2 mg/day (N=99) n (%) [EAIR]	Etrasimod > 2 mg/day (N=18) n (%) [EAIR]	Etrasimod Any Dose (N=1107) n (%) [EAIR]	Placebo (N=368) n (%) [EAIR]
Subject with at Least One Cardiac TEAE	24 (2.2) [0.03]	0	0	24 (2.2) [0.03]	1 (0.3) [<0.01]
Bradycardia	8 (0.7) [<0.01]	0	0	8 (0.7) [<0.01]	0
Sinus bradycardia	7 (0.6) [<0.01]	0	0	7 (0.6) [<0.01]	0
Atrioventricular block first degree	4 (0.4) [<0.01]	0	0	4 (0.4) [<0.01]	0
Atrioventricular block second degree	4 (0.4) [<0.01]	0	0	4 (0.4) [<0.01]	0
Ventricular extrasystoles	2 (0.2) [<0.01]	0	0	2 (0.2) [<0.01]	0
Sinus arrhythmia	1 (<0.1) [<0.01]	0	0	1 (<0.1) [<0.01]	0
Tachycardia	0	0	0	0	1 (0.3) [<0.01]

Appendix 13. Study APD334-003: Mean Change from Predose Baseline in hHR (ΔhHRPD) by Hour on Day 1 - Comparison of Study Treatments (HR set)



Study APD334-005: Mean Change from Predose Baseline in hHR (ΔhHRPD) by Hour on Day 1 - Comparison of Treatments Received During Parent Study APD334-003 (HR set)



RELEVANT REGULATORY BACKGROUND

Reference is made to all antecedent consultations from 05 FEB 2019, 15 OCT 2019, 20 AUG 2020, 08 AUG 2021, 13 OCT 2021, and 28 JUN 2022 providing recommendations to DG regarding the proposed safety analysis plan for etrasimod. Summaries of previous consults are provided below.

05 FEB 2019:

The data supported the sponsor's claim of a Day 1-only effect for heart rate reduction (approximate peak placebo-adjusted reduction of 10 bpm) and atrioventricular (AV) blocks. There was no significant QT prolongation. Heart rate reduction peaked at 1-4 hours. AV blocks (1st degree and 2nd degree type 1) were noted and unrelated to nadir heart rates. DCN recommended measuring heart rate, blood pressure, and performing an ECG at baseline and hourly for at least the initial 4 hours following drug administration.

15 OCT 2019:

DCN was requested to review the proposed protocol APD334-110, designed to determine whether a 5-day desensitization treatment strategy will attenuate the Day 1 transient negative chronotropic and dromotropic effects. The desensitization strategy involved administering 2 mg in various divided doses over different timespans within the 5-day desensitization period (fractions of 2 mg daily for 5 days totaling 2 mg at the end of the 5-day period; fractions of 2 mg every other day for 5 days totaling 2 mg at the end of the 5-day desensitization period, smaller fractions per hour for each of the 5 days, etc.). The proposed protocol required a 4-hour in-patient confinement period and continued Holter monitoring for 25 hours pre-dose and 24 hours post administration of the therapeutic dose (daily dose of 2 or 3 mg) following desensitization. The proposed protocol and associated safety features were deemed reasonable.

20 AUG 2020:

DCN was requested to review a new sponsor proposal to change the cardiac safety monitoring plan from a 4-hour post-dose in-clinic continuous ECG Holter and an additional post-discharge Holter for a 24-hour total observation period, to a discharge immediately after dosing with 24-hour remote Holter monitoring. The key change in the safety plan was a Holter-based patient-triggered attended surveillance (H+PTAS) program. Subjects would be instructed to contact the investigator immediately if symptoms occurred. This would prompt an immediate response from a 24-hour cardiac safety team, available to the investigator and subject(s), and would be led by the sponsor. Subjects with symptomatic cardiac events on Day 1 after dosing would be required to come to the clinic on Day 2 and at treatment re-initiation for pre-dose ECG and vital sign assessment to ascertain ongoing eligibility for the study. These subjects will be discharged with an additional 24 hours of H+PTAS post-dose.

DCN determined that the H+PTAS program would miss asymptomatic events that may also be clinically significant. The cardiac monitoring plan did not specify procedures designed to detect clinically significant arrythmias not related to a patient-initiated communication. DCN recommended 24-hour Holter monitoring in real-time by a central lab that would be alerted when

an arrhythmia was detected, and an on-call cardiologist to evaluate alerts and effectuate appropriate management.

08 AUG 2021:

DCN was requested to review the results of protocol APD334-110 designed to identify a desensitization strategy to minimize 1st dose cardiac effects. The data showed expected bradycardia and AV blocks (1st degree and 2nd degree type 1) that did not raise a clinical concern. There was no evidence of desensitization; there was no detectable distinction between various cohorts of divided dosing and timespans between dosing in attenuating nadir heart rates .

DCN was also asked to review the cardiac monitoring plan of the study APD334-210, a randomized, double-blind, placebo-controlled, 52-week trial to assess the efficacy and safety of etrasimod in 162 subjects with moderately active ulcerative colitis. Subjects would be randomized 2:1 (2 mg etrasimod: placebo). The trial would take place in North America, Europe, Asia Pacific, Middle East, and Africa. The cardiac monitoring plan addressed pre-treatment, first dose cardiac monitoring and clinic discharge criteria after cardiac monitoring, extended cardiac monitoring, study treatment discontinuation related to post-dose cardiac monitoring, and cardiac monitoring upon treatment re-initiation following dose interruption. The cardiac monitoring plan was deemed reasonable.

05-MAY-2022

DCN was asked to comment on the Sponsor's preliminary cardiac safety results presented in the pre-NDA briefing package dated May 4, 2022, to determine whether first-dose monitoring will be needed for the commercially marketed product. Based on DCN's review of the available data and since the first-dose effect of lower heart rate and atrioventricular block (1st and 2nd degree Mobitz 1, with no more advanced blocks) have been documented without clinically significant sequalae in multiple trials during drug development, a warning in the label may be sufficient without the need for a first-dose monitoring requirement for the commercially marketed product. However, our assessment will be finalized after review of the entire cardiovascular dataset.

CARDIAC SAFETY MONITORING IN PIVOTAL STUDIES

First-Dose Cardiac Monitoring

Based on the characterized first dose effects and earlier phase experience with the etrasimod development program, subjects were excluded from the phase 3 pivotal studies if they had any of the following cardiovascular conditions.

- Myocardial infarction, unstable angina, stroke or transient ischemic attack, decompensated heart failure requiring hospitalization or Class III/IV heart failure ≤ 6 months prior to or during the screening period
- History or presence of second-degree or third-degree AV block, sick sinus syndrome, or periods of asystole for > 3 seconds without a functional pacemaker
- History or presence of recurrent symptomatic bradycardia or recurrent cardiogenic syncope
- Screening or Week 0/Day 1 pre-randomization vital signs (sitting position) with a HR < 50 bpm or systolic BP < 90 mmHg or diastolic BP < 55 mmHg
- Screening or Week 0/Day 1 pre-randomization ECG with PR interval > 200 ms or
- QTcF ≥ 450 ms in men or ≥ 470 ms in women
- Start, stop, change, or planned change in dosage of any anti-arrhythmic drugs (Class I to IV) ≤ 1 week before screening or within 1 week before or after randomization

To further characterize the effect of etrasimod on heart rate and cardiac conduction, first-dose cardiac monitoring in the 2 pivotal Phase 3 UC studies included a baseline (pre-dose) ECG, 4-Hour (post-dose) ECG, vital signs (heart rate and blood pressure) at baseline and every hour for 4 hours, and in-clinic observation for at least 4 hours. If at the end of 4 hours a subject did not meet the *protocol-defined discharge criteria*, they underwent extended Day 1 monitoring and second dose monitoring on Day 2.

Protocol-defined discharge criteria

- HR ≥ 50 bpm or no more than 10 bpm lower than the pre-dose (baseline) value
- No evidence of second-degree AV block or higher

- No cardiac symptoms (e.g., chest pain, dizziness, palpitations, lightheadedness, shortness of breath, or syncope)

ECGs were also collected at Week 12, Week 52, and early termination (if applicable).
Vital signs were also collected prior to dosing at each study visit. First-dose cardiac monitoring was required following treatment interruptions of prespecified lengths.

The first-dose cardiac monitoring for the phase 2 study (APD334-003) in UC included in-clinic monitoring for at least 6 hours, safety ECG (pre-dose and at 6 hours post-dose), vital signs were recorded at baseline and hourly post-dose. If at the end of 6 hours a subject did not meet the protocol-defined discharge criteria, they underwent extended Day 1 monitoring.

Protocol-defined discharge criteria

- HR at hour 6 was the lowest since the first dose was administered or as deemed necessary by the Investigator due to a HR < 45 bpm,
- ECG showing new onset of second-degree or higher-grade AV block
- QTc interval ≥ 500 ms, or if a third-degree AV block occurred at any time
- Holter recordings were collected from 24 hours pre-dose through 24 hours post-dose on Day 1.
- ECGs were also recorded at screening and Weeks 0, 1, 2, 4, 8, and 12/exit from study.

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/s/

ROSALYN O ADIGUN
05/08/2023 09:52:53 AM

MARY R SOUTHWORTH
05/08/2023 10:02:16 AM

NORMAN L STOCKBRIDGE
05/08/2023 10:09:09 AM

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: March 3, 2023

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Team Lead, Cardiac Safety IRT, DCN

To: Anum Shami, RPM
DG

Subject: QT Consult to NDA 216956 (SDN 001)

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 11/8/2022 regarding the Review Division's QT related question. We reviewed the following materials:

- Sponsor's Summary of Clinical Pharmacology Studies (NDA216956 / SDN001)
- Previous IRT review for (b) (4) in DARRTS
- Sponsor's proposed labelling (NDA216956/SDN001)

1 Responses for the Review Division

Question from the review division: The Applicant included a thorough QT study report APD334-008 in the application. We would like to request an IRT-QT review of the thorough QT study and determine whether there are any QT prolongation concerns with the proposed drug that should be addressed in labeling/during the review.

IRT's response: The results from the TQT study indicated that etrasimod was not associated with significant QTc prolonging effect at a supratherapeutic dose of 4 mg on day 14 (i.e., 2 mg QD for 7 days, followed by 3 mg QD for 5 days and 4 mg QD for 2 days).

Below are our proposed edits to the label submitted to SDN001. Our changes are highlighted (addition, ~~deletion~~). Each section is followed by a rationale for the changes made. Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

(b) (4)

(b) (4)

We propose to use labeling language for this product consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance.

2 Internal Comments for the Division

- *None*

3 BACKGROUND

Etrasimod is a sphingosine 1-phosphate receptor modulator proposed for the indicated treatment of (b) (4) moderately to severely active ulcerative colitis. The recommended dose is 2 mg QD taken orally.

The QT prolongation potential of etrasimod was assessed in a through QT (TQT) study. The CS-IRT reviewed the TQT results previously (See the previous IRT review). The results from the TQT study indicated that etrasimod was not associated with significant QTc prolonging effect. The maximum tested dose of 4 mg on day 14 of multiple ascending doses (i.e., 2 mg QD for 7 days, followed by 3 mg QD for 5 days and 4 mg QD for 2 days) provided geometric mean Cmax of 155 ng/mL which was 1.8-fold of therapeutic Cmax. High clinical exposure scenario was not yet known at the time of the review.

In the current submission, the sponsor has presented results from assessments of the impact of intrinsic and extrinsic factors on etrasimod PK which indicates that none of the factors has a significant impact on etrasimod Cmax. Although hepatic impairment and co-administration with fluconazole (a dual CYP2C9 and 3A4 inhibitor) resulted in up to 1.57- and 1.84-fold increase in total AUC0-∞, respectively, none had impact on Cmax.

Based on the presented results, the high clinical Cmax for etrasimod (which is at steady state of 2 mg QD) was covered by the maximum tested dose in the TQT study.

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/

ELIFORD N KITABI
03/03/2023 01:23:25 PM

CHRISTINE E GARNETT
03/03/2023 01:42:22 PM

Medical Officer's Review of NDA 216956
Ophthalmology Consultation

NDA 216956

Submission date: 10/14/2022
Consult Request: 10/18/2022
Review date: 1/9/2023

Sponsor: Arena Pharmaceuticals Inc.

Drug Name: Etrasimod

Drug Class: Sphingosine 1-phosphate receptor modulator

Indications: Treatment of moderately to severely active ulcerative colitis

Consult Request: DG requests **Ophthalmology** reviewers for new NME NDA that arrived on 10/14/22; **PDUFA goal date: 10/14/23** NDA 216956 Etrasimod: NEW NME NDA (12-month clock-the program) **Purpose:** to review new marketing application: original NDA 216956, Etrasimod: NEW NME NDA (12-month clock the program) for the treatment of moderately to severely active ulcerative colitis **SharePoint: 10_14_22 NEW NME NDA Etrasimod-UC.** If you do not have access to the NDR- please email OND Informatics ONDInformatics@fda.hhs.gov ; share the NDR link and your email address and request access – they usually grant access within a few hours.
Submission links: EDR Link: \\NDA216956\0001

1) Please review the ophthalmology safety data that were submitted with this NDA in UC patients and comment on the acceptability of the proposed labeling (specifically, warnings and precautions and adverse reactions). Other drugs with similar mechanism include fingolimod, siponimod, ozanimod, and ponesimod. Ozanimod is approved for moderately to severely active UC.

2) Please plan to attend the midcycle meeting and labeling meetings related to Sections 5 and 6. Meeting dates are TBD – invites will be shared with the timeline.
A tentative timeline: Review Team and Planning

Reviewer's Comments: *Comments are limited to areas of ophthalmologic concern. Products in the same pharmacologic class (sphingosine 1-phosphate receptor modulators) are known to cause macular edema.*

Clinical Study: APD334-301: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, 52-Week Study to Assess the Efficacy and Safety of Etrasimod in Subjects with Moderately to Severely Active Ulcerative Colitis

Reviewer's Comments: *Ophthalmologic evaluations in this review are primarily limited to study APD334-301 because it is the only completed, 52-week, randomized comparison of Etrasimod.*

Study Design: The study design described is from the final protocol (Amendment 4.0/Original 0.0). Subjects were also enrolled under Protocol Amendments 1.0, 1.1, 3.0, 3.1, and 4.1. This was a multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of etrasimod 2 mg in subjects with moderately to severely active UC. Eligible subjects were randomized in a 2:1 ratio to receive either etrasimod 2 mg once daily or matching placebo once daily for up to 52 weeks, which included 12-Week and 40-Week Treatment Periods.

Enrolled and randomized: 433 subjects (etrasimod: 289; placebo: 144). Analyzed: 433 subjects in the Full Analysis Set (FAS), 424 subjects in the Modified FAS (mFAS; RB + stool frequency [SF]), 397 subjects in the mFAS (ES), 387 mFAS (MMS), 381 subjects in the mFAS (ES + Geboes Index), 394 subjects in the Week 12 Per Protocol Set, 365 subjects in the Week 52 Per Protocol Set, 433 subjects in the Safety Set, 287 subjects in the PK Set, and 283 subjects in the Biomarker Analysis Set.

Completed the study: 207 subjects (etrasimod: 161; placebo: 46)

Discontinued study: 226 subjects (etrasimod: 128; placebo: 98)

Schedule of Assessments – Screening and 12-Week Treatment Period

Evaluation	Screening Period	12-Week Treatment Period					2-Week Follow-Up Visit[b] ± 3 Days	4-Week Follow-Up Visit[b] ± 3 Days
	−28 to −1	W0 D1	W2 D15 ± 3 Days	W4 D29 ± 3 Days	W8 D57 ± 3 Days	W12 D85/ Early Termination[a] ± 3 Days		
Ophthalmoscopy with OCT	X[r]					X[r]	X[r]	
Study treatment administration		X – Once daily						

[a] All visits beyond W0/D1 may be virtual/hybrid visits (Section 9.6). Subjects discontinuing prior to Week 12/Day 85 should have an Early Termination (ET) visit within 7 days of the last study treatment administration and before initiation of any new treatments. For subjects who complete Week 12, the Week 12 visit was used to begin assessing eligibility for the APD334-303 OLE study.

[b] For subjects not participating in the APD334-303 OLE study, a follow-up visit was to be performed at 2 and 4 weeks after the last administration of study treatment. If the ET or Study Completion visit was ≥2 weeks after the last dose of study treatment, the 2-Week Follow-Up visit was not required; however, the 4-Week Follow-Up visit should have been scheduled and completed. If the ET or Study Completion visit was ≥4 weeks after the last administration of study treatment, the 4-Week Follow-Up visit was not required. If the absolute peripheral lymphocyte count was not within normal limits at the 4-Week Follow-Up visit, subjects should have returned for CBC with differential according to local standard of care (captured as subsequent Follow-Up visit or unscheduled visit).

[r] The Screening OCT should have been performed within the 28-day Screening Period. Subsequent ophthalmoscopy with OCT performed ± 7 days of the study treatment period and posttreatment period (i.e., 2-Week Follow-Up visit). OCTs occurring at the ET visit that were within 4 weeks of the last assessment (e.g., Week 12) were only required if clinically indicated. The 2-Week Follow-Up visit assessment was only required if clinically indicated. Details regarding ophthalmoscopy and OCT assessments are provided in Section 9.10.5.

Schedule of Assessments – 40-Week Treatment Period

Evaluation	40-Week Treatment Period							2-Week Follow- Up Visit[b] ± 3 Days	4-Week Follow- Up Visit[b] ± 3 Days
	W16 D113 ± 7 Days	W20 D141 ± 7 Days	W24 D169 ± 7 Days	W32 D225 ± 7 Days	W40 D281 ± 7 Days	W48 D337 ± 7 Days	W52 D365 ± 14 Days/ Early Termination[a] ± 7 Days		
Ophthalmoscopy with OCT[i]							X	X	
Study treatment administration[s]	X – Once daily								

[a] All visits beyond W0/D1 may be virtual/hybrid visits (Section 9.6). Subjects discontinuing treatment prior to Week 52/Day 365 should have had an Early Termination (ET) visit within 7 days of the last study treatment administration and before initiation of any new treatments. If a subject discontinued at or before Week 16, a sigmoidoscopy and biopsy were not required. For subjects with worsening disease or who completed Week 52 and wished to enter the APD334-303 OLE study, the Week 52/Early Termination visit was used to assess eligibility for the OLE study.

[b] For subjects discontinuing study treatment, 2-Week and 4-Week Follow-Up visits should have been scheduled 2-weeks and 4- weeks after the Week 52/Early Termination visit and the indicated assessments performed; however, if the ET or Week 52 visit was ≥ 2 weeks after the last dose of study treatment, the 2-Week Follow-Up visit was not required; however, the 4-Week Follow-Up visit should have been scheduled and completed. If the ET or Week 52 visit was ≥ 4 weeks after the last dose of study treatment, the 4-Week Follow up visit was not required. If the absolute peripheral lymphocyte count was not within normal limits at the 4-Week Follow up visit, subjects should have returned for CBC with differential according to local standard of care (captured as subsequent Follow-Up visit or unscheduled visit).

[i] Details regarding ophthalmoscopy and OCT assessments are provided in Section 9.10.5. The 2-Week Follow-Up visit assessment was only required if clinically indicated.

[s] On days with scheduled study visits, subjects should not have taken their dose of study treatment at home in order to complete pre-dose study procedures. The dose was to be taken at the study site after all pre-dose assessments and procedures have been completed.

Protocol: 9.10.5. Ophthalmoscopy and Optical Coherence Tomography

A complete ophthalmoscopy and OCT assessment will be performed according to the Schedules of Assessments. OCTs occurring at the ET visit that are within 4 weeks of the last assessment (e.g., Week 12) will only be required if clinically indicated. The 2-Week Follow-Up visit assessment is only required if clinically indicated. A standard visual acuity chart should be used for the visual acuity assessment. The OCT machine used should preferably not be changed during the study to allow for comparison of central foveal thickness measurements within each subject across timepoints.

Screening visit:

At the screening ophthalmology visit, the eye examination will include:

- Ophthalmologic history
- Best corrected visual acuity measurement (using Snellen chart internationally [if available])
- Ophthalmoscopy (may include contact lens biomicroscopy to examine the macula and optic disc). A dilated fundus exam should be performed in all subjects at the screening

visit and as needed at subsequent visits in subjects with significant abnormalities identified on the screening exam.

- Measurement of central foveal thickness by OCT (recorded in micrometers; required for all subjects regardless of the results of visual acuity or ophthalmoscopy)
- Slit lamp examination should be performed to establish uveitis disease status (yes/no). Uveitis should be characterized and graded using the Standardization of Uveitis Nomenclature criteria. Subjects with active uveitis without macular edema at Screening are eligible to enroll in the study.
- If there is a suspicion of macular edema by ophthalmoscopy and increased central foveal thickness by OCT, then additional testing should be considered at the discretion of the ophthalmologist (for example, fluorescein angiogram may be performed). Subjects with diagnosed macular edema at Screening should be deemed a screening failure and should not be randomized.
- Optional procedures in case of clinically significant abnormalities on ophthalmic exam may include but are not limited to:
  - Retinal photographs
  - Intraocular pressure

Scheduled post-screening visits:
At the scheduled ophthalmology visit, the eye examination will include

- Best corrected visual acuity measurement
- Ophthalmoscopy (may include contact lens biomicroscopy to examine the macula and optic disc)
- Measurement of central foveal thickness by OCT
- For subjects with uveitis findings on ophthalmic exam, additional testing should be considered (for example, fluorescein angiogram).

Subjects experiencing unexpected ophthalmic symptoms without a known suspected etiology or experiencing a relevant ophthalmic AE may need to have repeated ophthalmoscopy and OCT testing performed.

Applicant's Summary
12.5.4. Ophthalmology Examination Including Ophthalmoscopy and Optical Coherence Tomography

A complete ophthalmology examination (fundoscopy) including ophthalmoscopy and OCT assessment was performed as described in Study APD334-301 Protocol Section 9.10.5. There were no clinically meaningful differences between treatment groups in the following parameters evaluated at Baseline and at the Week 12 and Week 52 visits (Table 14.3.5.4.2): retinal photographs, intraocular pressure, CFT, slit lamp test, slit lamp examination result, slit lamp examination result details (Anterior chamber cells 0-4+; vitreous cells 0-4+; conjunctiva normal or abnormal; cornea normal or abnormal; Flare 0-4+, Haze 0-4+; Iris normal or abnormal; Lens normal or abnormal; Lids normal or abnormal); dilated fundus exam (normal, abnormal NCS, abnormal CS); dilated fundus exam details (macula normal or abnormal; optic nerve normal or abnormal; periphery normal or abnormal; vessels normal or abnormal).

The intraocular pressure and CFT were reported for each eye at Baseline and the Week 12 and Week 52 visit (Table 14.3.5.4.1). There were no clinically important differences in intraocular pressure between treatment groups in either eye at Week 12 and Week 52. At Baseline, the CFT was similar between treatment groups in both eyes. At Week 12, the mean (SD) change from Baseline in the left eye was −4.5 (25.45) μm with a range from −171 to 77 μm for placebo and 8.7 (54.82) μm with a range from −54 to 619 μm for Etrasimod (Table 14.3.5.4.1). In the right eye, the mean (SD) change from Baseline was −5.9 (24.73) μm with a range from −170 to 36 μm for placebo and 2.0 (22.62) μm with a range of −114 to 160 μm for etrasimod.

At Week 52, the mean (SD) change from Baseline in the left eye was 4.6 (20.80) μm with a range from −31 to 82 μm for placebo and 11.1 (31.22) μm with a range from −57 to 158 μm for etrasimod. In the right eye, the mean (SD) change from Baseline was 3.3 (19.55) μm with a range from −38 to 81 μm for placebo and 7.3 (26.25) μm with a range of −47 to 168 μm for etrasimod (Table 14.3.5.4.1). A higher proportion of subjects in the etrasimod group had increases in CFT > 40 μm in either eye (Week 12: etrasimod: 14 [8.6%]; placebo: 1 [1.2%]; Week 52: etrasimod: 14 [14.7%]; placebo: 1 [3.8%]; Table 14.3.5.5.1).

Reviewer's Comments: *The summary of ophthalmic findings submitted by the applicant is not accurate. There are imbalances between groups (Etrasimod vs Placebo) in abnormalities of the conjunctiva (4 vs 0), dilated fundus exam (26 vs 8), lens (25 vs 5), lids (9 vs 0),* ***retinal periphery (12 vs 0)****, and slit lamp examination (21 vs 5). The specific details for the type of abnormalities for all non-numeric findings have not been reported and many examinations were either not performed or not reported. Increases in macular thickness were more frequently reported in the Etrasimod group. Decreases in visual acuity were more frequently reported in the Etrasimod group than the Placebo group. Intraocular pressure was incorrectly classified as normal or abnormal. If appropriately classified, there were more subjects with elevated intraocular pressure during follow-up in the Etrasimod group than in the Placebo group. See details below.*

FDA Ophthalmology Reviewer's Findings:

Macular Thickness

Only 253 of the 433 subjects had optical coherence tomography (OCT) examinations in which the thickness of the macula was measured at baseline and at either Week 12, Week 52 or both. For subjects with OCT macular thickness reported at baseline, Week 12 and Week 52, **18%** (17/96) subjects on Etrasimod 2 mg **had increases of 40μm** (the predefined cutoff) compared to 8% (2/26) of the subjects on placebo. For the subjects with a baseline and Week 52, but not Week 12, 60% (3/5) of Etrasimod group had an increase in macular thickness compared to none in the placebo group. For the subjects with a baseline and Week 12, but not Week 52, 4% (3/72) of Etrasimod group had an increase in macular thickness compared to none (0/54) in the placebo group.

Decrease in visual acuity

The following 10 subjects (16 eyes) on Etrasimod had either a clinically significant decrease in visual acuity (doubling of the visual angle) or a best corrected visual acuity of 20/50 or worse without a baseline visual acuity. Only 2 subjects (2 eyes) met these criteria from the placebo group.

Etrasimod

(b) (6) right eye had visual acuity of 20/100 at Week 52 with no baseline recorded vision.
left eye had visual acuity of 20/100 at Week 52 with no baseline recorded vision.
right eye had visual acuity of 20/80 at Week 52 with baseline of 20/40 recorded vision.
right eye had visual acuity of 20/40 at Week 52 with baseline of 20/20 recorded vision.
right eye had visual acuity of 20/50 at Week 12 with baseline of 20/20 recorded vision.
left eye had visual acuity of 20/100 at Week 12 with baseline of 20/20 recorded vision.
right eye had visual acuity of 20/50 at Week 52 with no baseline recorded vision.
right eye had visual acuity of 20/200 at Week 52 with no baseline recorded vision.
left eye had visual acuity of 20/200 at Week 52 with no baseline recorded vision.
right eye had visual acuity of 20/50 at Week 52 with baseline of 20/20 recorded vision.
right eye had visual acuity of 20/50 at Week 12 with no baseline recorded vision.
left eye had visual acuity of 20/50 at Week 12 with no baseline recorded vision.
right eye had visual acuity of 20/63 at Week 52 with baseline of 20/20 recorded vision.
left eye had visual acuity of 20/63 at Week 52 with baseline of 20/20 recorded vision.
right eye had visual acuity of 20/50 at Week 12 with baseline of 20/20 recorded vision.
left eye had visual acuity of 20/50 at Week 12 with baseline of 20/20 recorded vision.

Placebo

(b) (6), left eye had visual acuity of 20/50 at Week 12 with no baseline recorded vision.
, right eye had visual acuity of 20/50 at Day 112 with no baseline recorded vision.

IOP

Classification between normal and abnormal was not consistent in the dataset. For example, none of the following was classified as abnormal:

SUBJID	VISITNUM	OEORRES	OEORRESU	OELAT
(b) (6)	1	22	mmHg	RIGHT
	6	22	mmHg	LEFT
	6	22	mmHg	RIGHT
	1	22	mmHg	LEFT
	1	22	mmHg	LEFT
	1	22	mmHg	RIGHT
	6	22	mmHg	LEFT
	1	22	mmHg	LEFT
	6	22	mmHg	RIGHT
	18.01	22	mmHg	LEFT
	18.01	22	mmHg	RIGHT
	1	22	mmHg	RIGHT
	1	22	mmHg	RIGHT
	1	22	mmHg	LEFT
	1	22	mmHg	RIGHT
	6	22	mmHg	LEFT
	1	23	mmHg	RIGHT
	13	23	mmHg	LEFT
	1	23	mmHg	LEFT
	6	24	mmHg	LEFT

However, the following were classified abnormal:

SUBJID	VISITNUM	OEORRES	OEORRESU	OELAT
(b) (6)	6	15	mmHg	LEFT
	6	15	mmHg	RIGHT
	6	24	mmHg	LEFT

Intraocular pressure above 21mmHg is generally considered abnormal. It is not clear why only one reading of 24mmHg was considered abnormal or why bilateral pressures of 15 were considered abnormal.

There were more post-baseline reports of elevated intraocular pressure in the Etrasimod group than in the Placebo group.

SUBJID	VISITNUM	OEORRES	OEORRESU	OELAT	Treatment Group
(b) (6)	13	22	mmHg	RIGHT	Etrasimod
	13	22	mmHg	LEFT	Etrasimod
	6	22	mmHg	LEFT	Etrasimod
	6	22	mmHg	RIGHT	Etrasimod
	6	22	mmHg	LEFT	Etrasimod
	6	22	mmHg	RIGHT	Etrasimod
	18.01	22	mmHg	LEFT	Etrasimod
	18.01	22	mmHg	RIGHT	Etrasimod
	6	22	mmHg	LEFT	Etrasimod
	13	23	mmHg	LEFT	Etrasimod
	13	24	mmHg	LEFT	Etrasimod
	6	24	mmHg	LEFT	Placebo
	6	25	mmHg	LEFT	Etrasimod
	13	30	mmHg	LEFT	Etrasimod
	13	30	mmHg	RIGHT	Etrasimod

While there were a number of subjects with elevated intraocular pressure, the use of corticosteroids in this population makes interpretation of elevated intraocular pressure extremely difficult.

Uveitis

The following individuals were reported to have inflammatory cells in either their anterior chamber of vitreous. They should be considered to have developed uveitis while on treatment with Etrasimod:

SUBJID	VISNUM	Inflammatory Cells
(b) (6)	6	2+ Cells
	6	2+ Cells

Elevated Intracranial Pressure
Subject (b) (6) developed increased intracranial pressure with optic nerve damage and permanently loss a significant level of visual acuity. The event should have been classified as Grade 3 instead of Grade 2 and there is insufficient justification to consider the event unlikely related to use of Etrasimod.

Proposed Labeling:

Reviewer's Comments: *The following labeling changes are recommended based on the submitted data:*

(b) (6)

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

Summary Recommendations:

1. Treatment with Etrasimod causes macular edema. The best estimate for the percentage of subjects with abnormal thickening of the macula is 18% in the Etrasimod vs 8% in the Placebo group.
2. The summary of ophthalmic findings submitted by the applicant is not accurate. There are imbalances between groups (Etrasimod vs Placebo) in abnormalities of the conjunctiva (4 vs 0), dilated fundus exam (26 vs 8), lens (25 vs 5), lids (9 vs 0), retinal periphery (12 vs 0), and slit lamp examination (21 vs 5). The specific details for the type of abnormalities for all non-numeric findings have not been reported and many examinations were either not performed or not reported. Increases in macular thickness were more frequently reported in the Etrasimod group. Decreases in visual acuity were more frequently reported in the Etrasimod group than the Placebo group.
3. Recommended labeling changes are provided in this review.

Wiley A. Chambers, MD
Supervisory Physician, Ophthalmology

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/s/

WILEY A CHAMBERS
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