ETRASIMOD RISK MANAGEMENT PLAN

RMP Version number: 3.0

Data lock point for this RMP: 02 August 2023 (clinical trials database)

11 October 2024 (post-marketing safety database)

Date of final sign off: 24 April 2025

Rationale for submitting an updated RMP: The main purpose of this RMP update is to support the alignment of the SmPC update with the CDS regarding the update for caution when co-administering etrasimod and anti-neoplastic, immune-modulating, or immunosuppressive (including corticosteroid) therapies to patients.

In addition, notable updates include information about the non-clinical text regarding the etrasimod M3 and M6 metabolites, corrections to 4 clinical exposure tables for the All UC Pool, and the inclusion of post-marketing data.

Actual protocol submission date, Interim report submission date, and Final study report submission date were added for C5041046.

Summary of significant changes in this RMP:

Part II, Module SII: The Cardiovascular section under Safety pharmacology was updated to include a statement that no effect on the hERG current was observed for the M3 and M6 metabolites when tested at up to 3.3 μM.

The Mechanism for Drug Interactions section under Other Toxicity-Related Information or Data was updated with text regarding the etrasimod metabolites M3 and M6 (2 diastereomers M3a/b and M6a/b); there is no risk of a perpetrator DDI due to M3a/b or M6a/b inhibition or induction of the major CYP/UGT enzymes and transporters at steady-state sub-nanomolar unbound exposures of M3 and M6 or several multiples of their unbound C_{max}.

Part II, Module SIII: Corrections to the total number of participants in the any dose group in 4 exposures tables (by duration, age and sex, race, and ethnicity) for the All UC Pool were updated in the exposure section only (Tables 4, 6, 8, and 10) and footnotes added.

Part II, Module SIV.3: Minor editorial changes were made to the patients with hepatic impairment section to correct previous typos.

Part II, Module SV: Post-authorisation exposure data were added.

Part II, Module SVII: Characterisation of the risk section for each risk was updated with the addition of post-marketing data.

Part III: Actual protocol submission date, Interim report submission date, and Final study report submission date were added for C5041046.

Part V.1: Under Serious opportunistic infections, Routine risk minimisation activities recommending specific clinical measures to address the risk, the existing caution text regarding co-administration of etrasimod and anti-neoplastic, immune-modulating, or immunosuppressive (including corticosteroids) therapies was updated as per the SmPC update.

Part VII, Annex 2: Actual protocol submission date, Interim report submission date, and Final study report submission date were added for C5041046.

Part VII, Annex 3: Study C5041046 was recategorized as an approved protocol.

Part VII, Annex 6: Under the Healthcare Professional Checklist, the existing bullet point "Anti-neoplastic, immune-modulating, or immunosuppressive therapies (including corticosteroids) should be co-administered with caution because of the risk of additive immune system effects during such therapy" was updated to "Caution should be used when co-administering etrasimod and anti-neoplastic, immune-modulating, or immunosuppressive (including corticosteroid) therapies to patients, because of the risk of additive immune system effects during such therapy," as per the SmPC update.

Part VII, Annex 8: Changes in version 3.0 were summarised.

Other RMP versions under evaluation: None.

Details of the currently approved RMP:

Version number: 2.0

Approved with procedure: EMEA/H/C/006007/II/0001

Date of approval (opinion date): 13 June 2024

QPPV name: Barbara De Bernardi, MD

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation applicant's QPPV. The electronic signature is available on file.

LIST OF ABBREVIATIONS

ADR	Adverse drug reaction
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AUC	Area under the time concentration curve
AUC_{inf}	Area under the concentration-time curve from time 0 to infinity
AUC_{last}	Area under the concentration-time curve from 0 to time of last measurable concentration
AV	Atrioventricular
BCRP	Breast cancer resistance protein
bpm	Beats per minute
BSEP	Bile salt export pump
CI	Confidence interval
C_{max}	Maximum concentration
COVID-19	Coronavirus disease 2019
CYP	Cyclooxygenase P450
EC	European Commission
ECG	Electrocardiogram
EEA	European Economic Area
eGFR	Estimated glomerular filtration rate
EPAR	European public assessment report
EU	European Union
FEV_1	Forced expiratory volume at 1 second
FVC	Forced vital capacity
GGT	Gamma-glutamyl transferase
GIRK	G-protein-gated inwardly rectifying potassium channel
GLP	Good Laboratory Practice
GVP	Guidelines on Good Pharmacovigilance Practices
HCP	Healthcare professional
hERG	Human ether-a-go-go-related gene
HIV	Human immunodeficiency virus
IARC	International Agency for Research on Cancer
IBD	Inflammatory bowel disease
IC_{50}	Half-maximal inhibitory concentration
INN	International non-proprietary name
JAK	Janus kinase
MAH	Marketing authorisation holder
MATE	Multidrug and toxin extrusion protein
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnet resonance imaging
mRNA	Messenger ribonucleic acid
n	Number
NOAEL	No observed adverse effect level
NOEL	No observable effect level
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
OLE	Open label extension
p-GP	P glycoprotein
PK	Pharmacokinetics
PL	Package leaflet
PML	Progressive multifocal leukoencephalopathy

PSUR	Periodic safety update report
PRES	Posterior reversible encephalopathy syndrome
PT	Preferred Term (MedDRA)
PY	Person-years
QPPV	Qualified Person Responsible for Pharmacovigilance
QTcF	Fridericia's corrected QT interval
RMP	Risk management plan
S1P	Sphingosine 1-phosphate
SAE	Serious adverse event
SmPC	Summary of product characteristics
SMQ	Standardised MedDRA Query
SMR	Standard mortality ratio
SOC	System Organ Class (MedDRA)
TBD	To be determined
TEAE	Treatment-emergent adverse event
TNF	Tumour necrosis factor
UC	Ulcerative colitis
UGT	Uridine 5'-diphospho-glucuronosyltransferase
ULN	Upper limit of normal
US	United States

TABLE OF CONTENTS

LIST OF TABLES

PART I. PRODUCT(S) OVERVIEW

Active substance(s) **(INN or common name)**	Etrasimod
Pharmacotherapeutic group(s) (ATC Code)	Sphingosine-1-phosphate (S1P) receptor modulators (L04AE05)
Marketing Authorisation Applicant	Pfizer Europe MA EEIG
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Velsipity
Marketing authorisation procedure	Centralised
Brief description of the product:	Chemical class: Etrasimod is a sphingosine 1-phosphate (S1P) receptor modulator that binds to S1P receptors 1, 4 and 5 ($S1P_{1,4,5}$) and is a balanced G-protein and beta-arrestin agonist at $S1P_1$.
	Summary of mode of action: Etrasimod partially and reversibly blocks the capacity of lymphocytes to egress from lymphoid organs, reducing the number of lymphocytes in peripheral blood thereby lowering the number of activated lymphocytes in the tissue. The mechanism by which etrasimod exerts therapeutic effects in ulcerative colitis (UC) is unknown but may involve the reduction of lymphocyte migration into sites of inflammation. The etrasimod-induced reduction of lymphocytes in the peripheral circulation has differential effects on leucocyte subpopulations, with greater decreases in cells involved in the adaptive immune response. Etrasimod has minimal impact on cells involved in innate immune response, which contribute to immunosurveillance.
	Important information about its composition: Not applicable.
Hyperlink to the Product Information:	Module 1.3.1 SmPC
Indication(s) in the EEA	Current:

	Velsipity is indicated for the treatment of patients 16 years of age and older with moderately to severely active UC who have had an inadequate response, lost response, or were intolerant to either conventional therapy, or a biological agent.
Dosage in the EEA	Current: The recommended dose is 2 mg taken orally once daily.
Pharmaceutical form(s) and strengths	Current: 2 mg film-coated tablet.
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II. SAFETY SPECIFICATION

Module SI. Epidemiology of the Indication(s) and Target Population(s)

Indication:

Treatment of patients 16 years of age and older with moderately to severely active UC who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biological agent.

Incidence:

Published incidence rates for UC differ considerably depending on geographical region, studied population, time period and case definition:

- In a prospective European collaborative study conducted in 1991-1993 and using a standardised case definition, the overall annual incidence of UC was estimated to be 10.4 cases per 100,000 population aged 15 to 64 years, with incidence rates ranging from 1.7 per 100,000 person-years in Portugal to 24.3 per 100,000 person-years in Iceland.[1] A prospective population based inception cohort study from 14 Western and 8 Eastern European countries reported a crude annual UC incidence in 2010 of 8.2 per 100,000 persons aged 15 years or older, with rates per 100,000 person-years in Western and Eastern European centres of 10.8 (range 2.9-31.5) and 4.1 (range 2.4-10.3), respectively.[2] A systematic review of European, population-based studies conducted between 1990 and 2016 reported annual incidence rates between 0.97 and 57.9 per 100,000 population.[3]

- For North America, population-based studies conducted in the 1980s or 1990s reported incidence estimates between 2.3 and 15.6 per 100,000 person-years.[4] Population-based studies conducted in North America in 1990 or later have annual reported incidence rates between 8.8 and 23.1 per 100,000 population.[3]

- Population-based studies conducted in Asian countries have, on average, reported lower incidence estimates between 0.2 per 100,000 person-years in the Philippines and 6.0 per 100,000 person-years in India.[3,4]

- Population-based studies conducted in Australia have reported incidence rates between 7.3 and 17.4 per 100,000 person-years.[3]

Throughout the 20th century, the incidence of UC steadily increased in North America, Europe, and Australia and, most recently, appears to be plateauing in these regions.[3] Since the 1990s, incidence has also been rising in newly industrialised countries in Africa, Asia, and South America.[3] Whether these trends are explained by changes in environmental exposures resulting from increasing urbanisation or by increased awareness and improved access to medical services is unclear.[3,5]

Prevalence:

A systematic review of population-based studies from 1990 or later reported the following UC prevalences:[3]

- For Europe, between 2.4 (Romania) and 505 (southeast Norway) per 100,000 population;
- For North America, between 140 (Quebec) and 286 (Olmsted County) per 100,000 population;
- For Asian countries, between 4.6 (Taiwan) and 57 (Japan) per 100,000 population; and
- For Australia, 196 per 100,000 population.

Considering that mortality in UC is low and the disease is most often diagnosed in the young, the global increase in incidence seen in recent years is likely to result in a corresponding increase in global prevalence.[5]

Demographics of the population in the authorised indication and risk factors for the disease:

UC has a bimodal pattern of incidence, with the main onset peak between ages 15 and 30 years and a second smaller peak between ages 50 and 70 years. Studies have noted either no preference regarding sex, or a slight predilection for men.[6] The few studies that evaluated race/ethnicity reported the greatest incidence of inflammatory bowel disease among white and Jewish people.[5] A family history of inflammatory bowel disease is the most important independent risk factor.[6]

Main existing treatment options:

Depending on disease activity and severity, pharmaceutical treatment options include 5-aminosalicylic acid derivatives, topical or systemic corticosteroids, cyclosporine, azathioprine or 6-mercaptopurine, antibodies including tumour necrosis factor (TNF) inhibitors (adalimumab, infliximab, golimumab), the anti-α4β7-integrin antibody vedolizumab and the anti-interleukin-12/-23 antibody ustekinumab, the Janus kinase (JAK) inhibitor tofacitinib and the S1P inhibitor ozanimod. The anti-interleukin-23 antibody mirikizumab was approved in the EU in 2023. Surgical treatment (colectomy) is necessary in about 10% of UC patients within 10 years of diagnosis; up to 30% of patients eventually need surgery.[6,7]

Natural history of the indicated condition in the (untreated) population, including mortality and morbidity:

The clinical course of UC is characterised by alternating periods of remission and relapse. At diagnosis, 30-50% of patients have disease confined to the rectum or the sigmoid colon

(distal colitis), 20-30% have left-sided colitis, and about 20% have pancolitis. Extension of colonic disease can occur in time.[6]

A meta-analysis of population-based inception cohort studies found no overall increased mortality in patients with UC compared with the general population (pooled standardised mortality ratio (SMR) 1.1; 95% CI 0.9, 1.2), although a greater risk of dying was observed during the first years of follow-up, in patients with extensive colitis, and in patients from Scandinavia.[8] A more recently published Canadian study reported statistically higher mortality due to any cause (SMR 1.21, 95% CI 1.12, 1.32) among UC patients compared to the general population.[9]

Important co-morbidities:

Table 1 provides a summary overview of comorbidities that have been reported to be associated with UC.

Table 1. Comorbidities (Potentially) Associated With Ulcerative Colitis

Musculoskeletal disorders	Ankylosing spondylitis, sacroiliitis, peripheral arthritis, rheumatoid arthritis, polymyalgia rheumatica[10,11,12,13,14]
Skin disorders	Erythema nodosum, pyoderma gangrenosum[10,15] Psoriasis[10,16]
Blood disorders	Anaemia[17,18,19,20,21]
Hepatobiliary disorders	Primary sclerosing cholangitis[10,15,22,23] Autoimmune hepatitis[10] Elevated liver function tests[24,25,26]
Respiratory disorders	Asthma[10,16,27]
Cardiovascular disorders	Arterial thromboembolism, cardiovascular disease, stroke[28,29,30] Venous thromboembolism[31,32,33,34,35,36]
Eye disorders	Uveitis, iridocyclitis[10,15]
Infections	Opportunistic infections[37,38] *Clostridium difficile* infection[39,40] Herpes zoster infection[41] Meningitis[42]
Malignancies	Any malignancy[43,44,45] Colorectal cancer[43,44,45,46,47,48,49,50] Neuroendocrine tumours[51]
Bone disorders	Osteoporosis / bone fracture risk[52]
Psychiatric disorders	Depression, anxiety disorders[53,54,55]

Note: For some disorders, results of epidemiological studies have been conflicting and an association with UC is not firmly established. See text for further details.

An association with UC is well-established for a number of specific, extraintestinal, immune-mediated inflammatory diseases, such as primary sclerosing cholangitis, erythema nodosum, pyoderma gangrenosum, ankylosing spondylitis, sacroiliitis, peripheral arthritis, anterior uveitis, and autoimmune hepatitis. The activity of these diseases can be either dependent or independent of bowel inflammation.[10,31]

Epidemiological studies have also reported associations with the following diseases that are discussed in RMP Module SVII as identified or potential risks of etrasimod:

Infections:

In a population-based cohort study conducted in France, the incidence of infections requiring hospitalisation among patients with inflammatory bowel disease (IBD) ranged from 8.4 per 1000 patient-years in adult patients unexposed to thiopurines and TNF inhibitors to 22.4 per 1000 patient-years in those exposed to thiopurine + TNF inhibitors combination therapy.[37] The risk of opportunistic infections ranged from 0.4 per 1000 patient-years in patients unexposed to thiopurines and TNF inhibitors to 4.1 per 1000 patient-years in those exposed to combination therapy.

A Canadian database study found a fivefold increased risk of *Clostridium difficile* infection among patients with UC compared with individuals without IBD.[39]

Increased risks among IBD patients compared with individuals without IBD have also been reported for herpes zoster infection[41] and meningitis.[42]

Cancer risk:

A Danish cohort study reported a standardised incidence ratio of 1.1 for overall cancer risk in UC patients compared with the general population.[43] Other studies, e.g., population-based cohort studies conducted in the Netherlands[44] or Italy,[45] did not report an increased overall cancer risk.

Epidemiological data are conflicting in regard to the risk of colorectal cancer in patients with UC. Several epidemiological studies have shown an approximately twofold increased risk of colorectal cancer in patients with UC compared with individuals without IBD,[31] with disease duration and severity, family history of colorectal cancer, and coexistent primary sclerosing cholangitis reported as risk factors.[46] Other studies did not find an increased colorectal cancer risk among UC patients.[43,44,45]

A population-based cohort study of all patients with IBD diagnosed in Norway and Sweden from 1987 to 2016 reported a 2-fold risk for small bowel neuroendocrine tumours in patients with UC.[51]

Hepatic disorders:

In an Italian retrospective review of patient records from IBD patients with no previous known liver disease, abnormal liver function tests were detected in 21% of patients. Most liver function test elevations were transient. Transient liver enzyme elevations were

considered attributable to immunosuppressant drugs in approximately one third of the cases; the cause was unknown in more than half of the cases. Persistent abnormal liver function was less common and most commonly attributed to fatty liver. Frequency of abnormal liver function was associated with duration of disease.[24]

In a Swedish prospective cohort study of patients with newly diagnosed IBD, abnormal liver function tests were detected in 46% of patients <17 years of age and in 30% of adults over a 5-year period. Causes included primary sclerosing cholangitis, autoimmune hepatitis, viral infections, hepatic cirrhosis, liver steatosis and adverse drug reactions (mainly azathioprine). In more than half of the cases with abnormal liver function tests, the abnormalities were temporary and no specific cause was found.[25]

In a case series of IBD patients attending a US IBD clinic, abnormal hepatic biochemistries were found in 29% of patients and not associated with IBD activity. The degree of enzyme elevation was mostly mild. An underlying chronic liver disease (mostly primary sclerosing cholangitis) was identified in approximately one fifth of the patients with abnormal hepatic biochemistries; in four fifths of these patients, no specific cause had been documented.[26]

Module SII. Non-Clinical Part of the Safety Specification

Etrasimod has been characterised in non-clinical safety studies including single-dose studies in CD-1 mice and beagle dogs; repeat-dose toxicity studies in CD-1 mice up to 3 months, Sprague Dawley rats up to 6 months, and beagle dogs up to 9 months. In addition, a complete genotoxicity testing battery, fertility and early embryonic development studies in Sprague Dawley rats, range-finding and definitive embryofoetal development studies in Sprague Dawley rats and New Zealand White rabbits, range-finding and definitive pre- and postnatal development studies in Sprague Dawley rats, range-finding and definitive juvenile toxicity studies in Sprague Dawley rats, carcinogenicity studies in CD-1 mice and Sprague Dawley rats and a 3T3 Neutral Red Uptake phototoxicity assay were conducted. All completed GLP toxicity studies used the clinically relevant route (oral) and schedule (daily) of administration. Sub-chronic and chronic toxicity studies included toxicokinetic evaluations (supported by validated bioanalytical methods) as well as assessments of recovery.

Table 2. Key Safety Findings and Relevance to Human Usage

Key Safety Findings from Non-Clinical Studies	Relevance to Human Usage
Repeat-Dose Toxicity	
Lymphoid Tissues	
The anticipated pharmacodynamic effects of S1P modulation on lymphoid cell populations and lymphoid tissues were seen in the mouse, rat and dog toxicity studies. All species exhibited etrasimod-related reductions in lymphoid cells in the periphery and in primary and secondary lymphoid tissues. Reductions were observed in mice (≥20 mg/kg/day), rats (≥25 mg/kg/day), and dogs (≥0.02 mg/kg/day) at respective exposures that were approximately 102 ×, 97 ×, and 0.58 × the human exposure at 2 mg/day.	Anticipated pharmacodynamic effect. Lymphopenia way also seen in clinical trials with etrasimod (see Module SVII). Regarding potential for associated clinical consequences in humans (infection risk, malignancy risk), see Module SVII.

Table 2. Key Safety Findings and Relevance to Human Usage

Key Safety Findings from Non-Clinical Studies	Relevance to Human Usage
Heart	
Non-adverse, etrasimod-related microscopic findings of vascular hypertrophy and hyperplasia in the tunica media were observed in the dog heart (at approximately ≥24 × the human exposure at 2 mg/day) in the 3-month and 9-month dog toxicity studies. These findings were non-adverse, without any evidence of related host compromise, including no associated vascular or perivascular inflammation, haemorrhage, thrombosis or necrosis, no associated myocardial degeneration or necrosis; no evidence of congestive heart failure, and no changes in the ECG.	Based on the high (24 ×) exposure multiples at which these effects occurred, no risk for patients is anticipated from these data. Regarding effects of etrasimod on heart rate, see below (cardiovascular safety pharmacology) and Module SVII.
Lung	
Increases in lung weight parameters were observed at exposures approximately ≥102 ×, ≥125 ×, and ≥5.9 × the human exposure at 2 mg/day in mice (up to 3 months), rats (up to 6 months), and dogs (up to 9 months), respectively. These increases were accompanied by alveolar histiocytosis in mice and dogs at exposures approximately ≥263 × and ≥5.9 ×, respectively, the human exposure at 2 mg/day. Non-adverse etrasimod-related fibrosis of the lung pleura was observed in the dog at doses ≥2 mg/kg/day (approximately ≥50 × the human exposure at 2 mg/day), which was reversible upon cessation of dosing. Fibrin deposition was also observed in the lung of mice at doses ≥20 mg/kg/day (approximately ≥102 × the human exposure at 2 mg/day). There were no functional consequences or morphologic changes observed in hypoxia-sensitive tissues (eg, brain) or sub-tissue compartments (eg, centrilobular areas in the liver). The increased lung weights and alveolar changes are consistent with a class effect of other approved S1P receptor modulators and are believed to be a result of increased vascular permeability in the lung.[56] In a respiratory safety pharmacology study in rats, acute oral administration of etrasimod resulted in no etrasimod-related effects on respiratory function.	There was no evidence of clinically significant effects on respiratory function (spirometry tests including) in the clinical studies with etrasimod (see Module SVII).
Liver	
Liver findings were noted only at high exposures. The minimum exposures at which these findings were observed in mice, rats, and dogs were approximately 102×, 76×, and 402×, respectively, the human exposure at 2 mg/day. At these exposures in etrasimod-dosed mice, rats, and dogs, increased liver weights, centrilobular/panlobular hepatocyte hypertrophy, liver cell necrosis, bile duct hyperplasia, and/or clinical pathology findings of increased serum total bilirubin concentration were observed. Changes in serum liver	Based on the high exposure multiples at which these effects occurred, no risk for patients is anticipated from these non-clinical data. Regarding potential for serious liver injury in humans, see Module SVII.

Table 2. Key Safety Findings and Relevance to Human Usage

Key Safety Findings from Non-Clinical Studies	Relevance to Human Usage
enzyme activities and serum cholesterol, total protein, globulin, and albumin concentrations were noted in etrasimod-dosed rats and dogs. Both species also experienced dose-related increases in coagulation parameters (activated partial thromboplastin time, prothrombin time) with no correlating evidence of an effect on haemostasis. All of the etrasimod-related effects on metabolic and coagulation parameters were non-adverse in animals and generally reversible upon cessation of dosing.	
Genotoxicity	
In genotoxicity studies, etrasimod was found to be neither mutagenic nor clastogenic.	No risk for patients based on these data.
Carcinogenicity	
Oral administration of etrasimod (0, 2, 6, or 20 mg/kg/day) to mice for up to 2 years resulted in an increased incidence of haemangiosarcoma or haemangiomas in males and females at ≥6 mg/kg/day. Systemic exposure at the NOEL of 2 mg/kg/day was approximately 19 × greater in mice than the human exposure at 2 mg/day. Oral administration of etrasimod (0, 2, 6, or 20 mg/kg/day) to rats for up to 2 years did not result in tumorigenic effects at any dose evaluated. In rats, systemic exposure to etrasimod at the highest dose level (20 mg/kg/day) was approximately 179× and 80× greater in females and males, respectively, than the human exposure at 2 mg/day.	A similar oncogenic effect in mice has been observed with other S1P receptor modulators. It is considered to be a result of molecular mechanisms that are considered mouse-specific and are likely irrelevant to humans.[57]
Phototoxicity	
Etrasimod did not demonstrate phototoxic potential in a 3T3 Neutral Red Uptake phototoxicity assay that measured the relative reduction in viability of BALB/c 3T3 mouse fibroblast cells when exposed to the test article (etrasimod and positive control promethazine) with and without ultraviolet radiation (Study TX16001).	Etrasimod is concluded to pose no phototoxic hazard to humans.
Reproductive and Developmental Toxicity	
In the embryofoetal development studies in rats and rabbits, administration of etrasimod during the period of organogenesis resulted in increased postimplantation loss and decreased mean litter numbers and proportions of viable foetuses in both species. Etrasimod-related external foetal malformations of localised foetal oedema, foetal anasarca, meningocele, short tail, and spina bifida were noted in rats ≥4 mg/kg/day. No external foetal malformations were noted in rats at 2 mg/kg/day. Etrasimod-related visceral malformations of the aortic arch, aorticopulmonary septal defect, and interventricular septal defect as well	The embryolethality and foetal malformations noted with etrasimod in the rat and rabbit embryofoetal development studies are consistent with similar findings and low exposure margins observed with approved S1P receptor modulators and are believed to be a result of the important role of $S1P_1$ receptors in embryogenesis, including vascular and neural development,[58] although etrasimod did not produce neural developmental effects in embryofoetal development, pre- and postnatal development or juvenile studies.

Table 2. Key Safety Findings and Relevance to Human Usage

Key Safety Findings from Non-Clinical Studies	Relevance to Human Usage
as a developmental variation of short brachiocephalic trunk were noted in rats ≥1 mg/kg/day. In rabbits, etrasimod-related visceral malformations of the 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. Based on these findings, the NOAELs for embryofoetal development were <1 mg/kg/day and 2 mg/kg/day in rats and rabbits, respectively. Maternal systemic exposure (AUC) at these developmental NOAELs corresponded to <5× and 0.8 × the human exposure at 2 mg/day for rats and rabbits, respectively. The NOAELs for maternal toxicity were 4 and 20 mg/kg/day for rats and rabbits, respectively, corresponding to approximately 21× and 11× the human exposure at 2 mg/day. In the definitive pre- and postnatal development study, parturition was affected at 4 mg/kg/day and maternal food consumption was reduced during lactation at 2 and 4 mg/kg/day, corresponding to a decrease in pup growth during the preweaning period. Between postnatal days 0-4, 7 and 3 pups were stillborn and 12 and 51 pups were found dead in the 2 and 4 mg/kg/day dose groups, respectively. Corresponding reductions in the viability index at 2 and 4 mg/kg/day and lactation index at 4 mg/kg/day were noted. Reductions in mean pup body weight values were noted from postnatal days 7-21 in all etrasimod-dosed groups. During the postweaning period, there were etrasimod-related decreases in mean body weight and mean food consumption in males at 4 mg/kg/day persisting from the preweaning period. A reduction in the mean number of implantations and an increased preimplantation loss were noted at 4 mg/kg/day in the F1 females at uterine examination. The NOAEL for maternal toxicity was 4 mg/kg/day, corresponding to 24× the human exposure at 2 mg/day. The NOAEL for parturition was 2 mg/kg/day, corresponding to 10× the human exposure at 2 mg/day. A preweaning NOAEL for the F1 generation could not be determined due to adverse effects on pup body weights at all dose levels. Finally, the postweaning F1 generation NOAEL for etrasimod was 2 mg/kg/day, corresponding to 5× the human exposure at 2 mg/day. In juvenile rats, etrasimod -related findings were consistent with the pharmacologic mechanism of action and with findings noted in adult rats in repeat-dose toxicity studies. There were no etrasimod-related effects on spermatogenesis or in males or on fertility and early	Etrasimod is therefore considered to be potentially teratogenic in humans. See Module SVII.

Table 2. Key Safety Findings and Relevance to Human Usage

Key Safety Findings from Non-Clinical Studies	Relevance to Human Usage
embryo development in females at any dose level evaluated.	
Safety pharmacology	
Cardiovascular	
In an in vitro hERG assay, etrasimod increased hERG current by 31.4% at 1 µM and 58.9% at 3 µM. An IC_{50} for hERG current inhibition could not be established since only increases in hERG channel current, rather than inhibition, were observed. No effect on the hERG current was observed for the M3 and M6 metabolites when tested at up to 3.3 µM. In an oral cardiovascular study in telemetered conscious dogs, etrasimod-related effects were limited to the highest dose tested (40 mg/kg; approximately 376× over the total C_{max} exposure at the human dose) and included transient, modest increases (compared to control) in systolic pressure (11.7%), diastolic pressure (14.2%), and mean arterial pressures (12.4%) noted 2 to 4 hours post-dose with no accompanying effects on pulse pressure. There were no etrasimod-related effects on heart rate, body temperature, or ECG parameters (qualitative or quantitative) at any dose level.	Blood pressure increase has been observed with other S1P receptor modulators in non-clinical studies and in humans and is further discussed in Module SVII. Although not observed in animals (i.e., mice, rats, or dogs), effects on heart rate and atrioventricular (AV) conduction have been noted in humans after administration of selective $S1P_1$ modulators. Bradycardia is further addressed in Module SVII.
Central Nervous System	
In a functional observational assessment conducted in male rats administered single oral doses of 25, 150, or 350 mg/kg etrasimod (estimated to correspond a total C_{max} 858× over the total C_{max} exposure at the human dose), neurobehavioral effects were limited to mild, transient exophthalmos at 30 and 90 minutes after administration of 350 mg/kg etrasimod that resolved by 150-minute post dose observation interval.	Based on the high exposure multiples at which these effects occurred, no risk for patients is anticipated from these non-clinical data. Potential neurological risk inferred from clinical trial data for drugs of this class are discussed in Module SVII. Neurological events such as posterior reversible encephalopathy syndrome (PRES), not reported in etrasimod clinical studies to date, but reported for other S1P receptor modulators, are described in the SmPC.
Respiratory	
In a respiratory plethysmography study conducted in male rats, acute oral administration of 25, 150, or 350 mg/kg etrasimod (estimated to correspond a total C_{max} 858× over the total C_{max} exposure at the human dose) resulted in no etrasimod-related effects on respiratory function, including respiratory frequency, tidal volume, and/or minute volume.	Based on the high exposure multiples at which these effects occurred, no risk for patients is anticipated from these non-clinical data.
Other Toxicity-Related Information or Data	
Mechanism for Drug Interactions	
Etrasimod is a substrate for cytochrome P450 (CYP) 2C8, CYP2C9, and CYP3A4 and to a lesser extent	Drug interaction via a single enzyme pathway will likely not result in a clinically relevant drug-drug interaction at therapeutic doses.

Table 2. Key Safety Findings and Relevance to Human Usage

Key Safety Findings from Non-Clinical Studies	Relevance to Human Usage
CYP2C19 and CYP2J2, and several uridine 5'-diphospho-glucuronosyltransferases (UGTs). Etrasimod (10 μM) was not a reversible or time-dependent inhibitor of CYP enzymes except that it was found to reversibly inhibit CYP2C8. However, the clinical risk of this inhibition is low as the calculated AUC ratio was less than the threshold value for a clinically relevant drug-drug interaction. Etrasimod was not an inhibitor of UGT1A3, UGT1A4, UGT1A9, UGT2B7, or UGT2B17 in vitro. Etrasimod was not an inducer of CYP1A2, CYP2B6, and CYP3A4 based on mRNA evaluations with etrasimod at 1 and 10 μM. Etrasimod was not a substrate of P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, nor an inhibitor of OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1, MATE-2K or BSEP. Etrasimod was found in vitro to inhibit P-gp, BCRP, and OATP1B1; however, the determined concentrations of the interacting drug were below both the gastrointestinal and systemic drug-drug interaction thresholds. Etrasimod metabolites M3 and M6 (2 diastereomers each M3a/b and M6a/b) exhibited are capable of in vitro enzyme interaction (i.e., CYP inhibition, CYP induction, and UGT inhibition) and transporter inhibition (gut, liver, and kidney). However at steady-state sub-nanomolar unbound exposures of M3 and M6 or several multiples of their unbound C_{max}, there is no risk of a perpetrator DDI due to M3a/b or M6a/b inhibition or induction of the major CYP/UGT enzymes and transporters. Based on the perpetrator data there is no expected interaction with the metabolites as victims in a DDI.	

Module SIII. Clinical Trial Exposure

As of the clinical trials data lock point of this RMP, etrasimod has been evaluated in clinical studies in patients with UC, alopecia areata, and atopic dermatitis. In addition, clinical studies have been conducted in healthy volunteers, subjects with hepatic impairment, and subjects with renal impairment. In accordance with the indication of the etrasimod marketing authorisation application, presentation of clinical study information in this RMP focuses on experience in the UC indication, with data provided for the following 2 safety pools:

1. Placebo-Controlled UC Pool: This pool includes Phase 2 study APD334-003 and the pivotal UC Phase 3 studies APD334-301, APD334-302, and APD334-308.

    - Study APD334-003 was a randomised, double-blind, placebo-controlled study in which patients received etrasimod 1 or 2 mg once daily for 12 weeks.

- Studies APD334-301 and APD334-302 were randomised, double-blind, placebo-controlled trials. Patients received etrasimod 2 mg or placebo once daily for a duration of 52 weeks and 12 weeks, respectively.

- Study APD334-308 was the randomised, double-blind, placebo-controlled extension study of APD334-302 in Japanese participants. Patients received etrasimod 2 mg or placebo once daily for a duration of 40 weeks following Week 12 visit of Study APD334-302 (total treatment duration of 52 weeks: 12 weeks in Study APD334-302 plus 40 weeks in Study APD334-308).

- In the 4 studies included in the Placebo-controlled UC pool, 577 subjects received at least one dose of etrasimod 2 mg, 52 received at least one dose of etrasimod <2 mg, and 314 received at least 1 dose of placebo and contributed 292.4, 11.4, and 119.0 subject-years of exposure, respectively.

2. All UC Pool: In addition to the 4 studies included in the Placebo-controlled UC pool, this pool includes studies APD334-005, APD334-303, and ES1011002 (open label period). Study APD334-005 was the open-label extension study for Phase 2 study APD334-003. In this study, patients received etrasimod 2 mg once daily for 34 weeks. Study APD334-303 is the ongoing open-label extension study for pivotal studies APD334-301 and APD334-302. In this study, patients are receiving etrasimod 2 mg once daily for up to 260 weeks. ES1011002 is an ongoing Phase 3 study in East Asian subjects with UC. Patients are receiving etrasimod 2 mg once daily for 12 to 40 weeks. Data from the open label period of this study are included in the All UC pool. In the 7 studies included in the All UC pool, 1165 subjects received at least one dose of 2 mg etrasimod, 52 subjects received at least one dose of <2 mg etrasimod, and 322 received at least 1 dose of placebo. Person-time of exposure was 1620 subject-years for 2 mg etrasimod, 11.4 subject-years for <2 mg etrasimod, and 125.6 subject-years for placebo.

In Module SVII of this RMP, reference is also made to the All Indications Pool, which includes 2 further studies in other indications than UC (APD334-201 in atopic dermatitis and APD334-205 in alopecia areata). In the 9 studies included in the All indications pool, 1430 subjects received at least one dose of etrasimod at any dose (including 1399 subjects who received at least one dose of etrasimod 2 mg), and 369 received at least 1 dose of placebo. Person-time of exposure for the All indications pool was 1830.8 subject-years for etrasimod (including 1747.8 subject years of etrasimod 2 mg) and 135.7 subject-years for placebo.

The cut-off date for all clinical trial exposure information presented in this section, as well as for the adverse event information presented in SVII.3 for the ongoing studies APD334-303 and ES101002 are 02 August 2023 and 30 August 2022, respectively (marketing application data snapshot date).

Information on clinical trial exposure in the placebo-controlled and All UC pools by duration, dose, age group, sex, race, and ethnicity is provided in Table 3 to Table 10.

Table 3. Exposure by Duration and Dose – Placebo-Controlled UC Pool

	Etrasimod Any Dose (N=629)		2 mg Etrasimod/day (N=577)		< 2 mg Etrasimod/day (N=52)		Placebo (N=314)		Total (N=943)	
Duration of Exposure Category [a]	n (%)	(PY)[b]	n (%)	(PY)[b]	n (%)	(PY)[b]	n (%)	(PY)[b]	n (%)	(PY)[b]
< 12 weeks	76 (12.1)	9.5	66 (11.4)	8.1	10 (19.2)	1.4	44 (14.0)	6.3	120 (12.7)	15.8
>= 12 to < 26 weeks	348 (55.3)	90.4	306 (53.0)	80.3	42 (80.8)	10.0	209 (66.6)	54.3	557 (59.1)	144.7
>= 26 to < 52 weeks	57 (9.1)	52.1	57 (9.9)	52.1	0	0	18 (5.7)	14.5	75 (8.0)	66.6
>=52 weeks	148 (23.5)	151.8	148 (25.6)	151.8	0	0	43 (13.7)	43.9	191 (20.3)	195.7
Total	629 (100.0)	303.8	577 (100.0)	292.4	52 (100.0)	11.4	314 (100.0)	119.0	943 (100.0)	422.7

Includes Studies: APD334-003, APD334-301, APD334-302, and APD334-308.
a. Number of days from first to and including last day of study treatment (Last Dosing Date - date of First Dosing Date +1).
b. Person Time (years) calculated by summing the years of exposure for a study in each treatment category.
PFIZER CONFIDENTIAL SDTM Creation: 29AUG2023 (11:16) Source Data: adex Table Generation: 16OCT2023 (08:46)
Output File: ./RMP/Etrasimod Ad Hoc Request scsc5040051a/adex_s02_aep_new

Table 4. Exposure by Duration – All UC Pool

	Etrasimod Any Dose (N=1179)		2 mg Etrasimod/day (N=1165)		< 2 mg Etrasimod/day (N=52)		Placebo (N=322)		Total (N=1539)	
Duration of Exposure Category [a]	n (%)	(PY)[b]	n (%)	(PY)[b]	n (%)	(PY)[b]	n (%)	(PY)[b]	n (%)	(PY)[b]
< 12 weeks	130 (11.0)	14.8	125 (10.7)	14.3	10 (19.2)	1.4	44 (13.7)	6.2	179 (11.6)	21.9
>=12 to <26 weeks	139 (11.8)	47.1	133 (11.4)	45.7	42 (80.8)	10.0	208 (64.6)	54.2	383 (24.9)	110.0
>=26 to <52 weeks	268 (22.7)	199.5	273 (23.4)	198.2	0	0	26 (8.1)	20.3	299 (19.4)	218.4
>=52 to <104 weeks	263 (22.3)	376.6	255 (21.9)	368.5	0	0	44 (13.7)	44.9	299 (19.4)	413.4
>=104 to <156 weeks	295 (25.0)	711.4	295 (25.3)	711.4	0	0	0	0	295 (19.2)	711.4
>=156 weeks	84 (7.1)	282.0	84 (7.2)	282.0	0	0	0	0	84 (5.5)	282.0
Total	1179 (100.0)	1632	1165 (100.0)	1620	52 (100.0)	11.4	322 (100.0)	125.6	1539 (100.0)	1757

Includes Studies: APD334-003, APD334-005, APD334-301, APD334-302, APD334-303 (02Aug2023 Snapshot), APD334-308 and ES101002 (30Aug2022 Snapshot).
a. Number of days from first to and including last day of study treatment (Last Dosing Date - date of First Dosing Date +1).
b. Person Time (years) calculated by summing the years of exposure for a study in each treatment category.
PFIZER CONFIDENTIAL SDTM Creation: 29AUG2023 (11:16) Source Data: adex Table Generation: 18MAR2024 (12:08)
Output File: ./RMP/scsc5040051b/adex_s02_aep_cp

1) "Etrasimod Any Dose" group counts unique participants exposed to Etrasimod of any dose since 38 participants were exposed to both 2 mg/day and < 2mg/day in the clinical programme.
2) "Total" group counts participants more than once if they were exposed to more than one dose.

Table 5. Exposure by Age Group and Sex – Placebo-Controlled UC Pool

	Etrasimod Any Dose (N=629)		2 mg Etrasimod/day (N=577)		< 2 mg Etrasimod/day (N=52)		Placebo (N=314)		Total (N=943)	
Age Group	Male n (%) (PY*)	Female n (%) (PY*)	Male n (%) (PY*)	Female n (%) (PY*)	Male n (%) (PY*)	Female n (%) (PY*)	Male n (%) (PY*)	Female n (%) (PY*)	Male n (%) (PY*)	Female n (%) (PY*)
Adolescents (16 to <18 years)	0	1(0.35) (0.3)	0	1(0.38) (0.3)	0	0	2(1.04) (1.2)	0	2(0.37) (1.2)	1(0.25) (0.3)
Adults (18 to <=64 years)	324(94.19) (149.5)	272(95.44) (136.7)	294(93.63) (143.2)	250(95.06) (131.7)	30(100.0) (6.3)	22(100.0) (5.1)	176(91.19) (66.6)	114(94.21) (43.8)	500(93.11) (216.1)	386(95.07) (180.6)
Elderly (>=65 years)	20(5.81) (10.9)	12(4.21) (6.4)	20(6.37) (10.9)	12(4.56) (6.4)	0	0	15(7.77) (4.1)	7(5.79) (3.3)	35(6.52) (15.0)	19(4.68) (9.6)
Total	344 (160.4)	285 (143.4)	314 (154.1)	263 (138.3)	30 (6.3)	22 (5.1)	193 (71.9)	121 (47.1)	537 (232.3)	406 (190.5)

Includes Studies: APD334-003, APD334-301, APD334-302, and APD334-308.
PY* Person Time (years) calculated by summing the years of exposure for a study in each treatment category.
PFIZER CONFIDENTIAL SDTM Creation: 29AUG2023 (11:16) Source Data: adex Table Generation: 16OCT2023 (08:46)
Output File: ./RMP/Etrasimod Ad Hoc Request scsc5040051a/adex_s02agesex

Table 6. Exposure by Age Group and Sex – All UC Pool

	Etrasimod Any Dose (N=1179)		2 mg Etrasimod/day (N=1165)		< 2 mg Etrasimod/day (N=52)		Placebo (N=322)		Total (N=1539)	
Age Group	Male n (%) (PY*)	Female n (%) (PY*)	Male n (%) (PY*)	Female n (%) (PY*)	Male n (%) (PY*)	Female n (%) (PY*)	Male n (%) (PY*)	Female n (%) (PY*)	Male n (%) (PY*)	Female n (%) (PY*)
Adolescents (16 to <18 years)	0	1(0.20) (2.3)	0	1(0.20) (2.3)	0	0	2(1.01) (1.2)	0	2(0.22) (1.2)	1(0.16) (2.3)
Adults (18 to 64 years)	639(93.42) (894.7)	471(95.15) (636.2)	631(93.34) (888.4)	465(95.09) (631.1)	30(100.0) (6.3)	22(100.0) (5.1)	180(90.91) (69.6)	117(94.35) (46.3)	841(93.03) (964.3)	604(95.12) (682.4)
Elderly (>=65 years)	45(6.58) (62.5)	23(4.65) (35.8)	45(6.66) (62.5)	23(4.70) (35.8)	0	0	16(8.08) (5.4)	7(5.65) (3.3)	61(6.75) (67.9)	30(4.72) (39.0)
Total	684 (957.2)	495 (674.2)	676 (950.9)	489 (669.2)	30 (6.3)	22 (5.1)	198 (76.1)	124 (49.5)	904 (1033)	635 (723.8)

Includes Studies: APD334-003, APD334-005, APD334-301, APD334-302, APD334-303 (02Aug2023 Snapshot), APD334-308 and ES101002 (30Aug2022 Snapshot).
PY* Person Time (years) calculated by summing the years of exposure for a study in each treatment category.
PFIZER CONFIDENTIAL SDTM Creation: 29AUG2023 (11:16) Source Data: adex Table Generation: 18MAR2024 (16:50)
Output File: ./RMP/scsc5040051b/adex_s02agesex_aep_cp

1) “Etrasimod Any Dose” group counts unique participants exposed to Etrasimod of any dose since 38 participants were exposed to both 2 mg/day and < 2mg/day in the clinical programme.
2) “Total” group counts participants more than once if they were exposed to more than one dose.

Table 7. Exposure by Race – Placebo-Controlled UC Pool

Race n(%)(PY*)	Etrasimod Any Dose (N=629)	2 mg Etrasimod/day (N=577)	< 2 mg Etrasimod/day (N=52)	Placebo (N=314)	Total (N=943)
American Indian Or Alaska Native	8 (1.3) (2.2)	7 (1.2) (2.2)	1 (1.9) (0.0)	4 (1.3) (1.6)	12 (1.3) (3.8)
Asian	72 (11.4) (43.1)	70 (12.1) (42.6)	2 (3.8) (0.5)	36 (11.5) (14.4)	108 (11.5) (57.4)
Black Or African American	8 (1.3) (3.6)	8 (1.4) (3.6)	0	6 (1.9) (3.0)	14 (1.5) (6.6)
Multiple	2 (0.3) (0.5)	1 (0.2) (0.3)	1 (1.9) (0.2)	0	2 (0.2) (0.5)
Not Reported	10 (1.6) (4.0)	10 (1.7) (4.0)	0	0	10 (1.1) (4.0)
White	528 (83.9) (250.2)	481 (83.4) (239.8)	47 (90.4) (10.5)	268 (85.4) (100.1)	796 (84.4) (350.3)
Other	1 (0.2) (0.2)	0	1 (1.9) (0.2)	0	1 (0.1) (0.2)
Total	629 (303.8)	577 (292.4)	52 (11.4)	314 (119.0)	943 (422.7)

Includes Studies: APD334-003, APD334-301, APD334-302, and APD334-308.
PY* Person Time (years) calculated by summing the years of exposure for a study in each treatment category.
PFIZER CONFIDENTIAL SDTM Creation: 29AUG2023 (11:16) Source Data: adex Table Generation: 16OCT2023 (08:46)
Output File: ./RMP/Etrasimod Ad Hoc Request scsc5040051a/adex_race_pcp

Table 8. Exposure by Race – All UC Pool

Race n (%) (PY*)	Etrasimod Any Dose (N=1179)	2 mg Etrasimod/day (N=1165)	< 2 mg Etrasimod/day (N=52)	Placebo (N=322)	Total (N=1539)
American Indian Or Alaska Native	10 (0.8) (13.5)	9 (0.8) (13.5)	1 (1.9) (0.0)	4 (1.2) (1.6)	14 (0.9) (15.1)
Asian	211 (17.9) (284.8)	211 (18.1) (284.3)	2 (3.8) (0.5)	36 (11.2) (14.4)	249 (16.2) (299.1)
Black Or African American	13 (1.1) (12.2)	13 (1.1) (12.2)	0	6 (1.9) (3.0)	19 (1.2) (15.2)
Multiple	2 (0.2) (3.2)	2 (0.2) (3.0)	1 (1.9) (0.2)	0	3 (0.2) (3.2)
Not Reported	10 (0.8) (15.6)	10 (0.9) (15.6)	0	0	10 (0.6) (15.6)
White	749 (63.5) (1191)	736 (63.2) (1180)	47 (90.4) (10.5)	276 (85.7) (106.7)	1059 (68.8) (1297)
Other	1 (0.1) (0.4)	1 (0.1) (0.1)	1 (1.9) (0.2)	0	2 (0.1) (0.4)
Unknown	183 (15.5) (111.1)	183 (15.7) (111.1)	0	0	183 (11.9) (111.1)
Total	1179 (1632)	1165 (1620)	52 (11.4)	322 (125.6)	1539 (1757)

Includes Studies: APD334-003, APD334-005, APD334-301, APD334-302, APD334-303 (02Aug2023 Snapshot), APD334-308 and ES101002 (30Aug2022 Snapshot).
PY* Person Time (years) calculated by summing the years of exposure for a study in each treatment category.
PFIZER CONFIDENTIAL SDTM Creation: 29AUG2023 (11:16) Source Data: adex Table Generation: 18MAR2024 (16:27)
Output File: ./RMP/scsc5040051b/adex_s02dem

1) "Etrasimod Any Dose" group counts unique participants exposed to Etrasimod of any dose since 38 participants were exposed to both 2 mg/day and < 2mg/day in the clinical programme.
2) "Total" group counts participants more than once if they were exposed to more than one dose.

Table 9. Exposure by Ethnicity – Placebo-Controlled UC Pool

Ethnicity n (%) (PY*)	Etrasimod Any Dose (N=629)	2 mg Etrasimod/day (N=577)	< 2 mg Etrasimod/day (N=52)	Placebo (N=314)	Total (N=943)
Hispanic Or Latino	26 (4.1) (8.8)	23 (4.0) (8.3)	3 (5.8) (0.5)	19 (6.1) (6.1)	45 (4.8) (14.9)
Not Hispanic Or Latino	599 (95.2) (293.1)	550 (95.3) (282.2)	49 (94.2) (10.9)	294 (93.6) (112.6)	893 (94.7) (405.8)
Not Reported	2 (0.3) (0.5)	2 (0.3) (0.5)	0	1 (0.3) (0.2)	3 (0.3) (0.8)
Unknown	2 (0.3) (1.3)	2 (0.3) (1.3)	0	0	2 (0.2) (1.3)
Total	629 (303.8)	577 (292.4)	52 (11.4)	314 (119.0)	943 (422.7)

Includes Studies: APD334-003, APD334-301, APD334-302, and APD334-308.
PY* Person Time (years) calculated by summing the years of exposure for a study in each treatment category.
PFIZER CONFIDENTIAL SDTM Creation: 29AUG2023 (11:16) Source Data: adex Table Generation: 16OCT2023 (08:46)
Output File: ./RMP/Etrasimod Ad Hoc Request scsc5040051a/adex_eth_pcp

Table 10. Exposure by Ethnicity – All UC Pool

Ethnicity n (%) (PY*)	Etrasimod Any Dose (N=1179)	2 mg Etrasimod/day (N=1165)	< 2 mg Etrasimod/day (N=52)	Placebo (N=322)	Total (N=1539)
Hispanic Or Latino	40 (3.4) (50.3)	39 (3.3) (49.8)	3 (5.8) (0.5)	19 (5.9) (6.1)	61 (4.0) (56.4)
Not Hispanic Or Latino	841 (71.3) (1352)	828 (71.1) (1341)	49 (94.2) (10.9)	302 (93.8) (119.3)	1179 (76.6) (1471)
Not Reported	3 (0.3) (6.7)	3 (0.3) (6.7)	0	1 (0.3) (0.2)	4 (0.3) (7.0)
Unknown	295 (25.0) (222.5)	295 (25.3) (222.5)	0	0	295 (19.2) (222.5)
Total	1179 (1632)	1165 (1620)	52 (11.4)	322 (125.6)	1539 (1757)

Includes Studies: APD334-003, APD334-005, APD334-301, APD334-302, APD334-303 (02Aug2023 Snapshot), APD334-308 and ES101002 (30Aug2022 Snapshot).
PY* Person Time (years) calculated by summing the years of exposure for a study in each treatment category.
PFIZER CONFIDENTIAL SDTM Creation: 29AUG2023 (11:16) Source Data: adex Table Generation: 18MAR2024 (16:28)
Output File: ./RMP/scsc5040051b/adex_s02dem2

1) "Etrasimod Any Dose" group counts unique participants exposed to Etrasimod of any dose since 38 participants were exposed to both 2 mg/day and < 2mg/day in the clinical programme.
2) "Total" group counts participants more than once if they were exposed to more than one dose.

Module SIV. Populations Not Studied in Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Important exclusion criteria of pivotal clinical studies APD334-301 and APD334-302 are discussed in Table 11 below. Regarding in- and exclusion criteria related to special populations, patients with inadequate haematological function or hepatic or renal impairment, see SIV.3.

Table 11. Summary of Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information? Rationale
Severe extensive colitis, current or recent toxic megacolon or bowel perforation; recent hospitalisation for exacerbation of UC requiring intravenous steroids.	These patients are at high risk for clinical interventions, potentially including colectomy. Inclusion of patients with these conditions could have affected study attrition or confounded study results.	No – exclusion of these patients was not related to a safety concern.
Crohn's disease, indeterminate colitis microscopic colitis, ischemic colitis.	These diseases are different from UC and were not the target indication. Inclusion of patients with these diseases might have confounded study results.	No – exclusion of these patients was not related to a safety concern. Also, these patients are not the target indication.
Positive assay or stool culture for pathogens or positive test for *Clostridioides difficile*; infectious colitis.	Concomitant intestinal infections could have confounded study results and, in view of the immunomodulatory effects of etrasimod, possibly would have put study participants at increased risk for worsening of infection.	No – (non-opportunistic) infections are discussed in SVII.1.1. The SmPC contraindicates etrasimod in patients with severe active infections or active chronic infections.
Pregnancy	S1P is involved in vascular growth and development during embryogenesis. Embryofoetal toxicity of etrasimod was seen in animal studies.	No – embryofoetal toxicity is an important identified risk of etrasimod (see Module SVII). The SmPC contraindicates etrasimod during pregnancy and in women of childbearing potential not using effective contraception.
Lactation	Precautionary measure considering also that etrasimod was found to be excreted in milk of treated animals.	No – whereas there are no data on the presence of etrasimod in human milk or potential effects on breastfed infants, there is no scientific rationale to assume a specific concern in this population and additional pharmacovigilance activities are currently not planned. The SmPC states etrasimod should not be used during breastfeeding.
Patients with conditions or receiving treatments that may affect cardiovascular function: • Myocardial infarction, unstable angina, stroke/transient ischemic attack, decompensated heart failure requiring hospitalisation or	As with other S1P receptor modulators, first administration of etrasimod may lead to transient bradycardia. Exclusion of patients with any of the listed conditions was a precautionary measure to minimise the risk for serious cardiovascular events.	No – bradycardia is a well-characterised risk of etrasimod (see SVII.1 for further information). The SmPC communicates this risk and recommends corresponding risk mitigation measures including contraindications for use in patients with certain cardiac conditions and pre-1st dose ECG for all

Table 11. Summary of Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information? Rationale
Class III/IV heart failure within 6 months or ongoing; • History or presence of second degree or third degree atrioventricular 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; • Presence of heart rate <50 bpm, systolic blood pressure <90 mm Hg or diastolic blood pressure <55 mm Hg; • Presence of PR interval >200 ms or Fridericia's corrected QT interval (QTcF) ≥450 ms in men or ≥470 ms in women; or • 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 randomisation.		patients and post-1st dose monitoring for specific patient populations. Caution should be applied when etrasimod is initiated in patients receiving treatment with a beta-blocker because of the potential additive effects on lowering heart rate. Similar caution should be applied if patients receive calcium-channel blockers, QT prolonging medicinal products, Class Ia and Class III anti-arrhythmic substances, since co-administration of these substances with etrasimod may lead to additive effects.
Forced expiratory volume at 1 second (FEV_1) or forced vital capacity (FVC) <70% of predicted values and FEV_1/FVC ratio <0.70 at screening.	Exclusion of these patients was a precautionary measure in consideration of reductions in FEV_1 and FVC observed with other S1P receptor modulators.	No – the potential for effects of etrasimod on respiratory function is discussed in SVII.1.1. The SmPC advises caution when using etrasimod in patients with severe respiratory disease.
History of macular oedema or retinopathy; uncontrolled diabetes or diabetes with significant comorbid conditions such as retinopathy.	Patients with a history of macular oedema or retinopathy might be at elevated risk for developing macular oedema when treated with S1P receptor modulators (see SVII.3.1.1). Patients with uncontrolled diabetes mellitus are at risk for developing diabetic retinopathy and thus might also be at elevated risk for macular oedema when treated with S1P receptor modulators.	No – macular oedema is an important identified risk of etrasimod (see Module SVII). The SmPC includes a warning that patients with a history of diabetes mellitus, uveitis, or underlying/coexisting retinal disease are at increased risk of macular oedema and recommends corresponding precautionary measures.
History or presence of active tuberculosis, recent or present clinically significant active infection	Because of their mechanism of action, S1P receptor modulators including etrasimod may	No – serious opportunistic infections are classified as an important potential risk of etrasimod (see

Table 11. Summary of Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information? Rationale
(e.g., serious and/or atypical), HIV infection, opportunistic infection including progressive multifocal leukoencephalopathy (PML), disseminated herpes simplex or disseminated herpes zoster, acute or chronic hepatitis B infection, current hepatitis C infection, or primary or secondary immunodeficiency; receipt of a live vaccine ≤4 weeks prior to randomisation.	increase the risk of exacerbation of opportunistic infections. Inclusion of patients with any of the listed conditions possibly would have put them at increased risk for development, recurrence, exacerbation or worse clinical outcomes of infection.	Module SVII). Corresponding risk minimisation measures, including contraindication of use in patients with severe active infections, active chronic infections, or are in an immunodeficient state are in the SmPC.
History of cancer (solid or haematological malignancies, except basal cell and in situ squamous cell carcinomas of the skin that have been excised and resolved) or colonic mucosal dysplasia; history of lymphoproliferative disorder, lymphoma, leukaemia, myeloproliferative disorder, or multiple myeloma.	In view of their immunomodulatory effects, it might be hypothesised that S1P receptor modulators interfere with cancer immunosurveillance, thereby increasing the risk for development or progression of malignancies. Increased risk of some malignancies has been reported for other S1P receptor modulators. Inclusion of these might have put them at increased risk for cancer recurrence or progression.	No – malignancy is classified as an important potential risk of etrasimod (see Module SVII). A corresponding warning is in the SmPC, and the SmPC contraindicates use of etrasimod in patients with active malignancy.
Clinically relevant neurological, endocrine, metabolic, psychiatric or other major systemic disease, cognitive impairment, alcohol or drug abuse.	Such conditions could impede implementation of the study protocol or interpretation of the study results.	No – exclusion of these patients was not related to a specific safety concern.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development program is, given its sample size and duration of follow-up at the time of submission, unlikely to detect certain types of adverse reactions such as rare adverse reactions or adverse reactions with a long latency (e.g., malignancies). Long-term safety data will continuously be collected via routine and additional pharmacovigilance activities, as described in PART III.

SIV.3. Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

There has been limited exposure to etrasimod in special populations and no epidemiology studies have been conducted in pregnant/lactating patients.

Table 12. Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of Special Population	Exposure
Pregnant women	There are no adequate and well-controlled studies on the use of etrasimod in pregnant or breast-feeding women. Pregnancy was an exclusion criterion of the etrasimod clinical studies and participating women of childbearing potential and/or their partners were required to use effective measures of contraception. A total of 19 pregnancies were reported from the clinical studies as of 02 August 2023. Please see Section SVII.3.1.2 for further information on pregnancies outcomes occurring in the etrasimod clinical trial program. Embryofoetal toxicity is classified as an important identified risk of etrasimod.
Breastfeeding women	Lactation was an exclusion criterion of the etrasimod clinical studies. There have been no reports of breastfeeding women/exposure via breast milk in the etrasimod clinical studies.
Patients with relevant comorbidities:	
• Patients with hepatic impairment	Adequate hepatic function (defined by a total bilirubin level ≤1.5 × upper limit of normal (ULN) range and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels ≤2.0 × ULN) was required for participation in the pivotal clinical studies APD334-301 and APD334-302. Etrasimod is primarily metabolised and eliminated hepatically. One pharmacokinetic study in hepatically impaired subjects has been completed (Study APD334-108). This Phase 1, open-label, single-dose, parallel-group study enrolled a total of 36 subjects who received etrasimod, including 8 subjects with mild impairment, 8 subjects with moderate impairment, 6 subjects with severe impairment, and 14 subjects with normal hepatic function. When compared with their respective normal matched controls, geometric mean C_{max} values were similar in the mild, moderate, and severe hepatic impairment groups. With increasing hepatic impairment, total geometric mean $AUC_{0-\infty}$ increased 13%, 29%, and 57% in the mild, moderate and severe hepatic function group, respectively, when compared with the normal matched hepatic function group. Unbound geometric mean $AUC_{0-\infty,u}$ were

Table 12. Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of Special Population	Exposure
	comparable for all hepatic impairment groups when compared with their respective normal matched control group. The increased etrasimod AUC in subjects with moderate and severe hepatic impairment is not expected to be clinically significant. No dose adjustment is necessary for patients with mild or moderate hepatic impairment. Etrasimod is contraindicated in patients with severe hepatic impairment. See SVII.3.1.6 regarding the potential for serious liver injury.
• Patients with renal impairment	Adequate renal function (defined by an estimated glomerular filtration rate ≥30 mL/min/1.73 m^2) was required for participation in the pivotal clinical studies APD334-301 and APD334-302. One pharmacokinetic study in subjects with severe renal impairment has been completed (Study APD334-112). In this Phase 1, open-label, randomised, single-dose study, C_{max} and AUC (both AUC_{last} and AUC_{inf}) were comparable between subjects with severe renal impairment (subjects with eGFR ≤29 mL/min) and healthy subjects. No dose adjustment are needed in patients with renal impairment.
• Patients with inadequate haematological function	Adequate haematological function (defined by white blood cell count ≥3.5 × 10^9/L with absolute neutrophil count (ANC) ≥1.5 × 10^9/L, lymphocyte count ≥0.8 × 10^9/L, platelet count ≥100 × 10^9/L, and haemoglobin ≥8 g/dL) was an inclusion criterion of the pivotal clinical trials. The SmPC advises to obtain a complete blood count, including lymphocyte count, before initiation of etrasimod and recommends assessment of complete blood count periodically during treatment. Regarding the important potential risk of (serious opportunistic) infections, see also SVII.3.1.4.
• Patients with cardiovascular impairment	Patients with significant cardiovascular comorbidities were excluded from the etrasimod clinical studies (for details, see SIV.1).
• Immunocompromised patients	Immunocompromised patients were excluded from the etrasimod clinical studies (for details, see SIV.1).
• Patients with a disease severity different from inclusion criteria in clinical trials	There is no clinical experience in this population.
Population with relevant different ethnic origin	Exposure by ethnic group is summarised in Module SIII. Approximately 80% of patients exposed to etrasimod in the clinical studies included in this RMP were white. No effects of ethnicity or race on the safety or benefit-risk profile of etrasimod are known.
Subpopulations carrying relevant genetic polymorphisms	No genetic polymorphisms relevant to the safety or benefit-risk profile of etrasimod are known and no such studies have been conducted.
Paediatric patients	Pivotal UC Phase 3 studies APD334-301 and APD334-302 allowed for enrolment of patients aged 16 to 80 years. Of the patients included in the All UC pool, 1 patient aged 16-17 years received etrasimod, contributing

Table 12. Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of Special Population	Exposure
	2.3 person-years of exposure. There is limited clinical study experience in patients younger than 16 years of age. Per the SmPC, etrasimod is indicated for treatment of patients 16 years of age or older. The SmPC informs that the safety and efficacy of etrasimod in paediatric patients aged below 16 years has not yet been established. Given the limited data in adolescents aged 16 and over, etrasimod should be used with caution especially when body weight is less than 40 kg due to the potential increased exposure.
Elderly patients	Pivotal UC Phase 3 studies APD334-301 and APD334-302 allowed for enrolment of patients up to 80 years of age. Of the 1539 patients included in the All UC pool, 91 patients were 65 years or older, of whom 68 patients received etrasimod. Total person-time in these 68 patients was 98.3 person-years. There are limited data available on patients over 65 years of age. No clinically significant differences of etrasimod were observed based on age. In the population pharmacokinetics (PK) analysis, no clinically significant differences in the PK of etrasimod based on age were observed. No dose adjustment is needed in patients over 65 years of age. The SmPC informs about the data limitations in this population. Safety in elderly patients ≥65 years of age, particularly with regard to infections, cardiovascular events, and eye affections is considered missing information in this RMP (see SVII.3.2.1) and a safety event of interest in the etrasimod PASS C5041046).

Module SV. Post-Authorisation Experience

SV.1. Post-Authorisation Exposure

SV.1.1. Method Used to Calculate Exposure

Etrasimod is being codeveloped by Pfizer and Everest Medicines Limited (hereafter referred to as Everest). Therefore, data from respective contractual parties from their designated territories are included as applicable. Everest territories include Macau and Singapore. Pfizer territories include all other markets including the EU, UK, and US.

For Pfizer territories, the worldwide exposure estimate is based on audited pharmacy and/or wholesaler sales of etrasimod received from IQVIA Health Midas Database. Assuming a regimen of 1 tablet daily, dividing total tablets sold by 365.25 days per year yields an estimate of total patient-years of exposure.

For Everest territories, the worldwide exposure estimate is based on the actual number of bottles sold. Assuming a regimen of 1 tablet daily, dividing total tablets sold by 365.25 days per year yields an estimate of total patient-years.

SV.1.2. Exposure

For Pfizer territories, cumulative estimated exposure by indication, gender, age group, dose, formulation, and region extrapolated from data provided by IQVIA[1] for the cumulative period from the International Birth Date (12 October 2023) through 11 October 2024 are summarized in Table 13. Please note that most of the ex-US product launches occurred in the second and third quarter of 2024. Since the exposure data is based on second quarter of 2024 and due to a possible lag in data of new product launches, only US data were available as of data-lock point.

Table 13. Cumulative Exposure for Etrasimod (International Birth Date to 11 October 2024) in Patient-Years for Pfizer Territories

Indication	Gender		Age (years)	Dose	Formulation	Region
	Female	Male	17-65	2 mg	Oral	United States
Ulcerative colitis	18	4	22	22	22	22

In Everest territories, 8 bottles were sold in Macau for the period from the International Birth Date (12 October 2023) through 11 October 2024. The estimated total patient-years exposure is 0.7 years.

Module SVI. Additional EU Requirements for the Safety Specification

Potential for misuse for illegal purposes

Given the mechanism of action of etrasimod and the lack of known pleasurable effects on the central nervous system, physiological or psychological dependency and resulting misuse for illegal purposes are not expected to occur with this medicine. Etrasimod has no known attributes that make it attractive for intentional overdose or illegal use. There have been no reports of abuse or misuse in the clinical studies. No concerns for abuse potential have been reported with other S1P receptor modulators.

[1] Of note, IQVIA data should not be regarded as complete sales information. Some countries where etrasimod is sold may not be covered by IQVIA. In addition, IQVIA requires a minimum threshold of sales after which it will start tracking a product; thus, data from countries where the product does not have sizeable sales would not be captured by IQVIA. Furthermore, IQVIA does not capture retail sales data and hospital data in all countries. Therefore, the sales volumes obtained through the use of IQVIA are likely to result in a large underestimate of the actual distributed product.

Module SVII. Identified and Potential Risks

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- **Lymphopenia, lymphocyte count decreased, lymphocyte percentage decreased:** Consistent with the known pharmacodynamic effect of S1P receptor modulators, etrasimod causes a reversible, dose-dependent reduction in peripheral lymphocyte count, which is observed within 2 weeks of initiating treatment. The SmPC informs that etrasimod causes a reversible sequestration of lymphocytes in lymphoid tissues and a mean reduction in peripheral blood lymphocyte count. The associated possible clinical outcome of serious opportunistic infections is included in this RMP as an important potential risk (see SVII.3.1.4).

- **(Non-serious / non-opportunistic) infections:** In the etrasimod clinical studies, the overall frequency of infections was similar in etrasimod-treated patients and patients who received placebo: In the Placebo-controlled UC pool 19.8% of etrasimod 2 mg-treated patients and 17.2% of patients in the placebo group had at least one treatment-emergent adverse event (TEAE) from the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) Infections and infestations. Exposure-adjusted incidence rates for any infection were 0.44 / person-year in the etrasimod 2 mg group and 0.53 / person-year in the placebo group, respectively. Serious infections were also not more common in etrasimod -treated patients than in the placebo group: In the Placebo-controlled UC pool, 0.7% of etrasimod 2 mg-treated patients and 1.6% of placebo-treated subjects had at least one serious TEAE from the SOC Infections and infestations. Exposure-adjusted incidence rates for serious infections were 0.01 / person-year for etrasimod and 0.04 / person-year for placebo, respectively. The more commonly reported events in both treatment groups were COVID-19 infections, urinary tract infections, and upper respiratory tract infections. There was also no indication of an increased risk of infections among etrasimod-treated patients compared with placebo-treated patients in the All indications pool. In view of the immunomodulatory properties of etrasimod, the SmPC informs that etrasimod may increase the susceptibility to infections. Serious opportunistic infections are included in this RMP as an important potential risk (see SVII.3.1.4).

- **Mildly or moderately elevated liver enzymes:** Similar to other S1P receptor modulators, hepatic enzyme elevations was more commonly observed during treatment with etrasimod than placebo. In the Placebo-controlled UC pool, median change from Baseline in ALT, AST, gamma-glutamyl transferase (GGT), and bilirubin was greater in the etrasimod 2 mg group compared with the placebo group at Week 12 and at Week 52, and more etrasimod-treated than placebo-treated subjects had shifts from normal to high

ALT, AST, GGT and bilirubin. Enzyme elevations were mostly mild to moderate and transient; there was 1 TEAE (0.2%) each of ALT increased, blood alkaline phosphatase increased, and liver function test abnormal leading to treatment discontinuation in etrasimod-treated patients and 1 TEAE (0.3%) of ALT increased leading to treatment discontinuation in placebo-treated subjects. No patient met the Hy's Law criteria of ALT or AST ≥3 × ULN with total bilirubin >2 × ULN. Serious hepatic adverse events were uncommon (see SVII.3.1.6). The SmPC informs that elevations of aminotransferases may occur in patients receiving etrasimod. Serious liver injury is included in this RMP as an important potential risk (see SVII.3.1.6).

Known risks that require no further characterisation and are followed up via routine pharmacovigilance:

- **Bradycardia:** In clinical studies with etrasimod, transient heart rate reduction was observed. In the etrasimod 2 mg group of the Pivotal UC Pool (where standardised monitoring was employed), decreases in heart rate by timepoint on Day 1 were largest in magnitude during the first 3 hours post dose (mean [standard deviation]: -7.2 [8.98] bpm). In the etrasimod 2 mg group, 76.5% of subjects achieved their heart rate nadir within 3 hours post dose and > 95% of subjects had heart rate nadir values ≥ 50 bpm. After Day 1, the effect of etrasimod on heart rate was either similar or progressively less with consecutive daily dosing. In the Pivotal UC pool, bradycardia/sinus bradycardia adverse events were reported from 5 (0.9%) and 4 (0.8%) of etrasimod 2 mg-treated subjects and none were reported from placebo-treated subjects. Overall, events of bradycardia reported from the clinical studies were without hemodynamic compromise and did not recur with consecutive doses. None of the bradycardia events were associated with serious clinical consequences such as cardiovascular events, syncope, fall or loss of consciousness. The SmPC includes risk minimisation messages commensurate to this risk, including a contraindication for use of etrasimod in patients with relevant cardiovascular comorbidities and recommendations to obtain an ECG in all patients prior to treatment initiation, to obtain cardiologist advice before initiation of etrasimod for certain patients with relevant pre-existing cardiovascular conditions, and for first-dose monitoring for at least 4 hours for signs and symptoms of symptomatic bradycardia in patients with relevant cardiovascular comorbidities.

- **Hypertension:** Transient, modest increases in systolic and diastolic blood pressure were observed in animals exposed to etrasimod (see Module SII). In the placebo-controlled clinical studies in UC, small increases in systolic blood pressure (1-2 mmHg relative to placebo) were observed. There were no clinically meaningful changes in diastolic blood pressure over time. Blood pressure increase was not progressive and resolved after treatment discontinuation. In the Pivotal UC pool, a larger proportion of patients in the etrasimod 2 mg group (2.5%, incidence rate 0.05 per person-year) had hypertension events compared to the placebo group (0.8%, incidence rate 0.02 per person-year). There were no serious adverse events (SAEs) of hypertension in UC patients (All UC pool). Similar increases in blood pressure have been observed with other S1P receptor modulators. Although the mechanism underlying blood pressure increase by S1P receptor agonists remains to be explored, current evidence suggests a non-cardiac

vascular action.[59] This risk is communicated in the SmPC where routine monitoring and management of blood pressure during treatment with etrasimod is recommended.

- **Bronchoconstriction:** Collective evidence from non-clinical safety pharmacology studies suggests that etrasimod does not affect respiratory function at therapeutic doses. In clinical trials, reductions in FEV_1 and FVC were observed in patients treated with etrasimod: In the Pivotal UC pool, a mean change in FEV_1 by -49 mL was observed in patients treated with etrasimod and by -19 mL in patients treated with placebo. There was no further decline of FEV_1 relative to placebo by week 52. The change in mean FVC in patients treated with etrasimod was -12 mL, compared to -5 mL for placebo by week 12 and -39 mL compared to 8 mL at week 52. The absolute change in mean FEV_1/FVC in patients treated with etrasimod was 0.026, compared to 0.024 for placebo. There was no further decline in mean FEV_1/FVC relative to placebo by week 52. No notable trends in respiratory or pulmonary adverse events were reported in clinical studies. Specifically, no adverse events of bronchoconstriction were reported and no clinically significant objective pulmonary function test abnormalities were observed in any patients from whom dyspnoea was reported as an adverse event. In view of the potential effects of S1P receptor modulation on vascular permeability[65,60] as well as non-clinical and clinical observations (in particular, decreased FEV_1) made with other S1P receptor modulators, the SmPC includes a warning that etrasimod should be used with caution in patients with severe respiratory disease (i.e., pulmonary fibrosis, asthma, and chronic obstructive pulmonary disease).

Bradycardia, hypertension, and effects on pulmonary function are class effects of S1P receptor modulators. There is no evidence of relevantly different clinical characteristics of these risks (e.g., in terms of frequency, severity, outcomes, or risk factors) in patients treated with etrasimod as compared with those treated with other S1P receptor modulators. These risks require no further characterisation and are followed via routine pharmacovigilance namely through signal detection and monitoring of adverse event reporting. The corresponding risk minimization messages in the product information are to be adhered to by prescribers (e.g., actions being part of standard clinical practice in each EU member state) where the product is authorised. No additional risk minimisation measures or additional pharmacovigilance activities are proposed for any of these risks. For these risks, the product information for other S1P receptor modulators includes risk minimisation messages that are similar to those proposed for etrasimod, with no indication that these messages are not adhered to by prescribers. For each of the above risks, the recommended risk minimisation actions are therefore considered to be part of standard clinical practice.

In conclusion, bradycardia, hypertension and bronchoconstriction are not likely to have a negative impact on the risk-benefit balance of the product. In accordance with GVP guidance, these risks are concluded not to qualify as a “Risk considered important for inclusion in the list of safety concerns in the RMP” for etrasimod.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

The important identified and potential risks considered important for inclusion in the list of safety concerns of this RMP are summarised in Table 14. Important identified risks are those events for which the totality of the scientific evidence is sufficient for a causal association to the product and are considered to have an impact on the benefit-risk profile of the product. Important potential risks are those events for which the level and/or totality of the evidence, after thorough evaluation of the data, as described above, were not judged sufficient to classify the risk as "identified" but are still considered important and for which additional characterization is needed. Further information on each of the important risk is provided in SVII.3.

Table 14. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risk	Scientific Evidence	Risk-Benefit Impact
Important Identified Risks		
Macular oedema	Downmodulation of endothelial $S1P_1$ by S1P receptor modulators has been hypothesised to compromise the blood-retina barrier and thereby trigger the development of macular oedema, especially in patients with pre-existing impaired barrier function such as patients with diabetic retinopathy. There were no ocular findings (adverse or non-adverse) in animals exposed to etrasimod. Macular oedema was infrequently observed in patients treated with etrasimod 2 mg in the clinical studies.	As has been observed with other S1P receptor modulators, occurrences of macular oedema in patients treated with etrasimod have been reported. These events have been generally reversible upon drug discontinuation. Effects of macular oedema on central vision would have a negative impact on the risk-benefit profile of etrasimod in affected patients. Additional pharmacovigilance activities and additional risk minimization measures are planned for this risk (see III.2 and V.2).
Embryofoetal toxicity	S1P is involved in vascular growth and development during embryogenesis. Embryofoetal toxicity of etrasimod was seen in animal studies. There are a limited amount of data from the use of etrasimod in pregnant women.	Based on animal data, potential clinical consequences could include an increased risk of foetal loss or malformations. Additional pharmacovigilance activities and additional risk minimization measures are planned for this risk (see III.2 and V.2).
Important Potential Risks		
Symptomatic bradycardia (including conduction disorders)	In the Placebo-controlled UC pool, a total of 11 participants (1.9%) who received etrasimod 2 mg experienced 12 bradycardia events (PT Bradycardia/Sinus bradycardia). In the All UC pool, a total of 21 participants (1.8%) who received etrasimod 2 mg experienced bradycardia events (PT Bradycardia/Sinus bradycardia). Two participants in the UC clinical development program, in pivotal UC studies, experienced bradycardia with	The impact of this risk on the risk-benefit balance of the product is low. Overall, events of bradycardia and AV blocks reported from the clinical studies were without hemodynamic compromise and did not recur with consecutive doses. None of these events, including symptomatic events, were associated with serious clinical consequences such as cardiovascular events, syncope, fall or loss of consciousness. No second degree AV

Table 14. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risk	Scientific Evidence	Risk-Benefit Impact
	associated symptoms on study Day 2. One participant experienced bradycardia and dizziness (both moderate [Grade 2] in severity) and one participant experienced mild (Grade 1) bradycardia, dizziness, and palpitations. No treatment for these events was administered and the events resolved for both participants. In the Placebo-controlled UC pool, a total of 4 participants (0.6%) experienced TEAEs of Atrioventricular block (AV block). Two of the participants had first degree AV block (1 mild, 1 moderate event) and 2 had second degree AV block Mobitz type I (1 mild, 1 moderate event). None of the participants had symptoms associated with the events of AV block. In the All UC pool, a total of 8 participants (0.7%) experienced AV block; 4 of these participants /events were not previously reported in the Placebo-controlled UC pool. One of the participants in the All UC pool experienced symptoms of dizziness and chest tightness concurrently with the event of AV block second degree Mobitz type I. The event of AV block resolved and no treatment was given for the event. There were no events of bradycardia or AV block of clinical consequence, e.g. no syncope or falls.	blocks Mobitz type II or higher were reported. Additional pharmacovigilance activities and additional risk minimization measures are planned for this risk (see III.2 and V.2).
Serious opportunistic infections	Because of their mechanism of action, S1P receptor modulators including etrasimod may increase the risk of infections, potentially including serious opportunistic infections. Opportunistic infections were uncommon in the placebo-controlled UC studies, mostly mild or moderate in severity and resolved without discontinuation of etrasimod. Two opportunistic infections were reported as SAEs from the open label UC study (APD334-303): one case each of herpes simplex meningitis and cytomegalovirus colitis in etrasimod-treated patients; both events resolved with antiviral treatment. PML has been observed in patients with multiple sclerosis treated with other S1P receptor modulators. No case of suspected	In principle, opportunistic infections may be serious and, in rare cases, fatal. When diagnosed early and treated appropriately, opportunistic infections generally have a favourable outcome. PML has not been reported from the etrasimod clinical studies. Additional pharmacovigilance activities and additional risk minimization measures are planned for this risk (see III.2 and V.2).

Table 14. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risk	Scientific Evidence	Risk-Benefit Impact
	or confirmed PML has been observed in etrasimod-treated patients.	
Malignancy	In view of their immunomodulatory effects, it might be hypothesised that S1P receptor modulators interfere with cancer immunosurveillance, thereby increasing the risk for development or progression of malignancies. In the etrasimod clinical studies, the overall incidence of malignancies was consistent with the frequency expected in the general population. However, the number of exposed patients and duration of follow-up is considered too small for definitive conclusions.	If confirmed, the impact of this risk would be determined by the magnitude of treatment-attributable risk, type of malignancy, timing of detection, and treatment options. Additional pharmacovigilance activities and additional risk minimization measures are planned for this risk (see III.2 and V.2).
Serious liver injury	Similar to other S1P receptor modulators, liver enzyme elevations were more commonly observed during treatment with etrasimod than placebo. These enzyme elevations were mostly mild to moderate and mostly resolved while continuing treatment (see above, SVII.1.1). In the All UC pool, there was 1 serious hepatic adverse event (Hepatic enzyme increased) in etrasimod-treated patients and 1 hepatic SAE (Jaundice) in placebo-treated patients; neither of these SAEs was assessed as drug-related. No patient met the Hy's Law criteria of ALT or AST ≥3× ULN with total bilirubin >2× ULN. The mechanism by which S1P receptor modulators might cause hepatic enzyme elevations is not known.	Clinical trial data show that treatment with etrasimod, like other S1P receptor modulators, might be associated with liver enzyme elevations. The currently available non-clinical and clinical data do not provide evidence that etrasimod causes serious liver injury. However, considering that cases of serious liver injury have been reported in patients treated with other S1P receptor modulators and in view of the limited exposure in the etrasimod clinical studies, the presence of such a risk and a corresponding impact on the benefit-risk profile of etrasimod should be further evaluated. Additional pharmacovigilance activities and additional risk minimization measures are planned for this risk (see III.2 and V.2).
Neurological events of PRES or convulsion	Neurological events such as posterior reversible encephalopathy syndrome (PRES) and convulsion are included in the RMPs of other S1P receptor modulators as important potential risks. These events were observed in multiple sclerosis populations; confounding by indication or a risk specific to patients with pre-existing cerebral disease are therefore considered a possibility. However, PRES has also been associated with other immunomodulatory agents (e.g., cyclosporine, tacrolimus) in other clinical contexts. Considering also the potential effects of S1P receptor modulators on endothelial function, a	The impact of this risk on the risk-benefit balance of the product would likely be low considering that patients experiencing PRES or convulsion usually recover if the cause is removed and supportive treatment is promptly initiated. Additional pharmacovigilance activities and additional risk minimization measures are planned for this risk (see III.2 and V.2).

Table 14. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risk	Scientific Evidence	Risk-Benefit Impact
	potential causal association should be further evaluated. Per data lock point of this RMP, there have been no cases of PRES in the etrasimod clinical studies. One case of post stroke seizure was reported as an SAE from the open label UC study (APD334-303) in an etrasimod-treated patient with a history of cerebral infarction, hypercholesterolaemia, hypertension, ischaemic stroke, and post stroke seizure. In response to the event, antiepileptic medication was adjusted; the event resolved.	
Missing Information		
Safety in elderly patients ≥65 years of age, particularly with regard to infections, cardiovascular events and eye affections	Limited number of elderly patients in the clinical studies conducted with etrasimod.	Experience with treatment of elderly patients in the etrasimod clinical development program is limited and considering the potential impact of immunomodulatory and cardiovascular effect of etrasimod on elderly patients (in view e.g. of their frailty) are therefore not fully characterised. Additional pharmacovigilance activities are planned for this risk (see III.2). This is a safety event of interest in the etrasimod PASS C5041046.

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

Details of the important identified risks, important potential risks, and missing information of etrasimod are presented in the following tables. Adverse event information from clinical studies is shown for the 2 clinical study pools for which exposure is summarised in Module SIII, i.e., the Placebo-controlled UC pool and the All UC pool. In addition, data from the All indications pool, which includes 2 further studies in other indications than UC, are presented where relevant. Pertinent adverse events were identified by applying predefined MedDRA searches. The corresponding MedDRA search criteria are presented in each table. All data were coded in MedDRA version 24.1. The same cut-off date as used in Module SIII (02 August 2023) was applied.

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

SVII.3.1.1. Important Identified Risk: Macular Oedema

SVII.3.1.1.1. Potential mechanisms

S1P receptor subtypes contribute to regulation of endothelial barrier function. Down-modulation of endothelial $S1P_1$ by S1P receptor modulators has been hypothesised to compromise the blood-retina barrier and thereby trigger the development of macular oedema especially in patients with pre-existing impaired barrier function such as patients with (diabetic) retinopathy.[65]

SVII.3.1.1.2. Evidence source and strength of evidence

Events of macular oedema have been reported in the etrasimod clinical studies and have been reported for other S1P receptor modulators.

SVII.3.1.1.3. Characterisation of the risk

Clinical Trials

Four subjects experienced events of macular oedema in the etrasimod clinical program. Three subjects (2 subjects in the etrasimod 2 mg group and 1 subject in the placebo group in the Placebo controlled UC pool) experienced 1 event each of macular oedema and 1 subject (in the All UC pool) experienced 2 events of cystoid macular oedema. All events were mild or moderate in severity.

Of the 5 events of macular oedema/cystoid macular oedema observed in the etrasimod UC clinical trials, 3 events were resolved/resolving, 1 event was not resolved (still present) at the time of the report, and the outcome for 1 event was unknown. Three subjects (2 in the etrasimod 2 mg group and 1 in the placebo group) had predisposing conditions (2 subjects had uveitis and 1 subject had foveal cyst and retinal haemorrhage). There were no pertinent events reported in subjects in the < 2 mg etrasimod group.

The frequency, severity, seriousness, and outcomes of macular oedema reported in the clinical trials are summarised in Table 15 below. There were no pertinent events in the <2 mg etrasimod group.

Table 15. Macular Oedema: Frequency, Severity, Seriousness and Outcomes of Adverse Events in Clinical Trials

	Placebo-controlled UC Pool		All UC Pool	
	Etrasimod 2 mg	**Placebo**	**Etrasimod 2 mg**	**Placebo**
Number of patients with at least one adverse event n (%)	2	1	3	1
Number of adverse events n (%)	2	1	4[a]	1
Incidence rate of adverse events per 100 patient-years (95% CI)	0.20 (0.02, 0.71)	0.80 (0.02, 4.48)	0.18 (0.04, 0.53)	0.78 (0.02, 4.32)
Maximum severity[b]				
Mild	1	1	1	1

Table 15. Macular Oedema: Frequency, Severity, Seriousness and Outcomes of Adverse Events in Clinical Trials

	Placebo-controlled UC Pool		All UC Pool	
	Etrasimod 2 mg	**Placebo**	**Etrasimod 2 mg**	**Placebo**
Moderate	1	0	2	0
Severe	0	0	0	0
Maximum seriousness[c]				
Non-serious	2	1	3	1
Serious	0	0	0	0
Latest outcome[d]				
Resolved	2	0	3	0
Still present	0	1	0	1
Fatal	0	0	0	0
Unknown	0	0	0	0
Reported events (MedDRA PTs)				
Macular oedema	2	1	2	1
Cystoid macular oedema	0	0	1	0

a. Please note, 1 subject reported 2 events of Cystoid macular oedema; all other subjects had 1 event each.
b. For the same adverse event of interest, the most severe case was selected in this summary.
c. For the same adverse event of interest, the most serious case was selected in this summary.
d. For the same adverse event of interest, the last case was selected in this summary. If last case has a missing outcome, the case is considered still present.

Table displays number of adverse events, except for the first row which displays number of patients with at least one event.
Incidence Rates: Number of subjects with events per 100 patient-years.
Placebo-controlled UC Pool includes studies: APD334-003, APD334-301, APD334-302, and APD334-308.
All UC Pool includes studies: APD334-003, APD334-005, APD334-301, APD334-302, APD334-303 (02Aug2023 Snapshot), APD334-308 and ES101002 (30Aug2022 Snapshot).
Source: Table 51a.1.5.0.2, Table 51a.2.5.0.2, Table 51a.1.5.4, Table 51a.1.6.4, Table 51a.1.7.4, Table 51a.2.5.4, Table 51a.2.6.4, Table 51a.2.7.4.

Post-marketing

Table 16. Macular Oedema: Reported Events, Seriousness, and Outcomes from Post-Marketing Cases

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Macular oedema	5	5	0	0	0	0	0	5
Total	5	5	0	0	0	0	0	5

F = fatal; H = hospitalisation; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; R = resolved/resolving; RS = resolved with sequelae; NR = not resolved; U = unknown

SVII.3.1.1.4. Risk factors and risk groups

For the non-selective S1P receptor modulator fingolimod, it has been hypothesised that patients with pre-existing impaired blood-retinal barrier function, e.g., patients with a history of diabetes mellitus, uveitis, or underlying/coexisting retinal disease, may be at elevated risk of developing macular oedema.

SVII.3.1.1.5. Preventability

An ophthalmic evaluation of the fundus, including the macula, is recommended near the start of treatment in all patients and at any time if there is any change in vision while taking etrasimod. It is recommended that patients with a history of diabetes mellitus, uveitis, or retinal disease undergo an ophthalmic evaluation near treatment initiation with etrasimod and have follow up evaluations while receiving therapy. Follow-up evaluations of at-risk patients while receiving therapy and ophthalmic evaluation of any patient who reports a change in vision during treatment with etrasimod are suitable measures for detection of this event and initiation of adequate corrective measures will mitigate the risk of unfavourable outcomes.

SVII.3.1.1.6. Impact on the risk-benefit balance of the product

S1P receptor modulator-induced macular oedema appears to be generally reversible upon treatment discontinuation.[61,62,63]

Macula oedema is a medically important event; effects of macular oedema on central vision would have important clinical consequences and a negative impact on the risk-benefit profile of etrasimod in affected patients.

SVII.3.1.1.7. Public health impact

With measures for appropriate patient selection and monitoring in place, cases of permanent impairment due to this event are expected to be rare and the public health impact therefore to be low.

SVII.3.1.1.8. MedDRA terms

PTs Cystoid macular oedema; Macular oedema.

SVII.3.1.2. Important Identified Risk: Embryofoetal Toxicity

SVII.3.1.2.1. Potential mechanisms

S1P is involved in vascular growth and development during embryogenesis. Embryofoetal toxicity of etrasimod was seen in animal studies, including a higher proportion of post-implantation loss, lower foetal weights as well as external visceral malformations and developmental variation in rats, and increased post-implantation loss, foetal malformations and skeletal developmental variations in rabbits. The exposure margin for the rat embryo-foetal development study (relative to human clinical exposures) was <5 ×; for rabbits it was 0.8 × (see Module SII).

SVII.3.1.2.2. Evidence source and strength of evidence

This risk is inferred from non-clinical data. There are a limited amount of data from the use of etrasimod in pregnant women.

SVII.3.1.2.3. Characterisation of the risk

Clinical Trials

Based on animal data, clinical consequences could include an increased risk of foetal loss or malformations.

As of 02 August 2023, a total 19 pregnancies have been reported in the etrasimod clinical development program (all indications), including 13 pregnancies with etrasimod female subject exposure and 8 pregnancies in female partners of male study subjects.

Of the 19 pregnancies, there have been 6 live births (4 healthy babies, 1 full term baby with neonatal jaundice, and 1 premature baby at 34 weeks with neonatal jaundice and patent foramen ovale); there have been 5 spontaneous abortions, 4 elective terminations [redacted], 2 cases for which no data are available on pregnancy outcomes, 1 anembryonic gestation (umifenovir was co-suspect), and 1 ectopic pregnancy.

Post-marketing

Table 17. Embryofoetal Toxicity: Reported Events, Seriousness, and Outcomes from Post-Marketing Cases

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Maternal exposure during pregnancy	1	0	0	0	0	0	0	1
Total	1	0	0	0	0	0	0	1

F = fatal; H = hospitalisation; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; R = resolved/resolving; RS = resolved with sequelae; NR = not resolved; U = unknown

SVII.3.1.2.4. Risk factors and risk groups

Other than women of childbearing potential who are not using effective contraception, no specific risk factors or risk groups for embryofoetal toxicity subsequent to etrasimod exposure are known.

SVII.3.1.2.5. Preventability

Counselling of women of childbearing potential about this risk, availability of a negative pregnancy test result prior to initiating treatment with etrasimod, requirement to use effective contraception during treatment and for at least 14 days after treatment discontinuation, and avoidance of use of etrasimod in pregnant women are considered suitable measures to minimise this risk.

SVII.3.1.2.6. Impact on the risk-benefit balance of the product

Whereas the exact magnitude of risk in case of maternal exposure to etrasimod during pregnancy is unknown, this risk can be readily managed by preventing intrauterine exposure and thus has no major impact on the risk-benefit balance of the product.

SVII.3.1.2.7. Public health impact

The magnitude of risk for embryofoetal toxicity in case of maternal exposure to etrasimod during pregnancy is unknown. However, with implementation of appropriate risk management, pregnancies in women treated with etrasimod are expected to be rare, and the public health impact of this risk is therefore expected to be low.

SVII.3.1.2.8. MedDRA terms

SMQ Pregnancy and neonatal topics (narrow).

SVII.3.1.3. Important Potential Risk: Symptomatic Bradycardia (Including Conduction Disorders)

SVII.3.1.3.1. Potential mechanisms

S1P receptor modulators have transient negative chronotropic and dromotropic effects, which are attributed to activation of G-protein-gated inwardly rectifying potassium (GIRK) channels in cardiac myocytes. Effects are most pronounced following the first administered dose and generally subside with consecutive doses. This phenomenon is thought to be due to gradual internalisation of S1P on cardiac myocytes.[64,65,66]

SVII.3.1.3.2. Evidence source and strength of evidence

This potential risk is inferred from the mechanism of action of S1P receptor modulators and clinical study data.

SVII.3.1.3.3. Characterisation of the risk

Clinical Trials

In both the Placebo-controlled UC and All UC pools, all participants with TEAEs of bradycardia and AV conduction delay subcategories were in the etrasimod 2 mg group.

All participants who experienced bradycardia TEAEs remained haemodynamically stable and none had events of clinical consequence (e.g., syncope, loss of consciousness).

Two participants, both in the Placebo-controlled UC pool, experienced bradycardia events accompanied by symptoms. One participant experienced TEAEs of bradycardia (HR of 44 bpm) and dizziness (both moderate [Grade 2] in severity) on study Day 2; no treatment was administered for the events, which resolved on study Day 4. One participant experienced TEAEs of bradycardia on study Days 1 and 2; the event on study Day 2 was accompanied by symptoms of dizziness and palpitations. All events were mild in severity; no treatment for the events was given and the events resolved same day (study Day 2). Both participants were discontinued from study due to the bradycardia events.

TEAEs of AV block were experienced by a total of 4 participants (0.6%) in the Placebo-controlled UC pool who received etrasimod 2 mg (none in <2 mg etrasimod or placebo groups) with onset on Study Day 1 post dose. Two participants had events of AV block first degree (1 event was mild, 1 was moderate); study treatment was withdrawn for the participant who had a moderate (Grade 2) event, the event was not resolved at time of reporting; for the other participant, study treatment was not changed, and the event resolved. Two participants had events of AV block second degree Mobitz type I (1 event was mild, and 1 was moderate); study treatment was withdrawn in response to the event for the participant who had the moderate (Grade 2) event; the other participant continued on study treatment. Both events resolved. None of the events were accompanied by symptoms.

In the All UC pool a total of 8 participants (0.7%) who received etrasimod 2 mg (none in <2 mg or placebo groups) experienced one event each of AV block, with onset on Study Day 1 post dose. An additional 4 participants experienced events in this pool, not previously reported in the Placebo-controlled UC pool. Two of these participants had events of AV block first degree; both events were mild (Grade 1); study treatment was not changed and both events resolved. Two participants experienced an event of AV block second degree (Mobitz type I). In the first case, the event was accompanied by symptoms of dizziness and chest tightness at hour 2 and 3 post first dose on Day 1 with a HR of 48 bpm at Hour 3. The event was reported as an SAE, study treatment was discontinued and the event resolved on Day 2. No treatment was given for the event. In the second case, the event (was confirmed as second degree AV block (Mobitz type I) and first detected on Day 1 post dose Holter monitoring, assessed as not serious and related to study drug. The study drug was discontinued and the event was resolving.

No participants in the Placebo-controlled UC pool or All UC pool experienced TEAEs of AV block second degree Mobitz type II or higher.

One participant in the etrasimod 2 mg group experienced a TEAE of arrhythmia in the All UC pool; the event was mild (Grade 1) in severity; no action was taken with the study drug and the event resolved.

Post-marketing

Table 18. Symptomatic Bradycardia (Including Conduction Disorders): Reported Events, Seriousness, and Outcomes from Post-Marketing Cases

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Bradycardia	14	6	4	0	4	0	1	9
Arrhythmia	2	2	0	0	0	0	0	2
Atrioventricular block first degree	1	0	0	0	0	0	0	1
Sinus bradycardia	1	1	1	0	1	0	0	0
Total	18	9	5	0	5	0	1	12

F = fatal; H = hospitalisation; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; R = resolved/resolving; RS = resolved with sequelae; NR = not resolved; U = unknown

SVII.3.1.3.4. Risk factors and risk groups

Patients with particular medical history and/or concomitant medications in whom bradycardia may be poorly tolerated; this may include, for example, patients with second degree AV block Mobitz type II or higher AV block, history of symptomatic bradycardia or recurrent syncope, patients with significant QTcF prolongation (QTcF ≥450 msec in males; ≥ 470 msec in females), patients with cerebrovascular disease, patients with history of myocardial infarction or congestive heart failure. The initiation of a beta blocker with stable treatment of etrasimod has not been studied. The effect of co-administration of etrasimod and a calcium channel blocker has not been studied.

SVII.3.1.3.5. Preventability

Prior to initiation of treatment with etrasimod, obtaining an ECG in all patients to assess for pre-existing cardiac abnormalities and obtaining cardiologist advice in patients with relevant pre-existing cardiovascular conditions are suitable measures to reduce the probability of this safety concern.

First dose monitoring in patients with certain pre-existing cardiac conditions for 4 hours is a suitable measure for detection of this event and initiation of appropriate management observation until the resolution of the symptoms/findings will mitigate the risk of unfavourable outcomes.

Caution should be applied when etrasimod is initiated in patients receiving treatment with a beta-blocker because of the potential additive effects on lowering heart rate. Similar caution should be applied if patients receive calcium-channel blockers, QT prolonging medicinal products, Class Ia and Class III anti-arrhythmic substances, since co-administration of these substances with etrasimod may lead to additive effects.

SVII.3.1.3.6. Impact on the risk-benefit

The potential impact of this risk on the risk-benefit balance of the product is considered low. Symptomatic bradycardia may cause dizziness or fainting, which may result in injury due to falls; however, in etrasimod clinical trials, subjects who experienced bradycardia or AV block events were generally asymptomatic and events were transient. In patients who experienced symptoms, such as dizziness, most symptoms were mild and symptoms resolved without intervention.

SVII.3.1.3.7. Public health impact

With measures for appropriate patient selection and monitoring in place, clinical sequelae from this event are expected to be rare and the public health impact therefore to be low.

SVII.3.1.3.8. MedDRA terms

PTs Adams-Stokes syndrome; Arrhythmia; Atrial conduction time prolongation; Atrial escape rhythm; Atrioventricular block; Atrioventricular block complete; Atrioventricular block first degree; Atrioventricular block second degree; Atrioventricular dissociation; Atrioventricular node dysfunction; Bradyarrhythmia; Bradycardia; BRASH syndrome; Cardiac telemetry abnormal; Central bradycardia; Conduction disorder; Electrocardiogram ambulatory abnormal; Electrocardiogram PR prolongation; Maximum heart rate decreased;

Nodal arrhythmia; Nodal rhythm; Peripheral pulse decreased; Pulse abnormal; Sinoatrial block; Sinus arrest; Sinus bradycardia; Sinus node dysfunction; Trifascicular block

SVII.3.1.4. Important Potential Risk: Serious Opportunistic Infections

SVII.3.1.4.1. Potential mechanisms

The mechanism of action of etrasimod and other S1P receptor modulators includes a reduction of certain lymphocyte subpopulations in peripheral blood, which could be hypothesised to be associated with an increased risk of infections. In the clinical studies, treatment with etrasimod was not associated with an increased risk of infections overall, of serious infections, or of serious opportunistic infections. This might be explained by the specificity of etrasimod on immune cell populations. For example, whereas peripheral blood B cells [$CD19^+$] and T cells [$CD3^+$], T-helper [$CD3^+CD4^+$], and T-cytotoxic [$CD3^+CD8^+$] cell subsets were all reduced, natural killer cells and monocytes were not; moreover, T-helper cells were more sensitive to the effects of etrasimod than T-cytotoxic cells.

SVII.3.1.4.2. Evidence source and strength of evidence

This potential risk is inferred from the mechanism of action of etrasimod and clinical study data.

SVII.3.1.4.3. Characterisation of the risk

Clinical Trials

The frequency, severity, and outcomes of serious opportunistic infections reported in the clinical trials are summarised in Table 19 below. There were no pertinent events in the <2 mg etrasimod group.

Table 19. Serious Opportunistic Infections: Frequency, Severity, Seriousness and Outcomes of Adverse Events in Clinical Trials

	Placebo-controlled UC Pool		All UC Pool	
	Etrasimod 2 mg	**Placebo**	**Etrasimod 2 mg**	**Placebo**
Number of patients with at least one adverse event n (%)	0	0	1 (0.1%)	0
Number of adverse events n (%)	0	0	2 (0.2%)	0
Incidence rate of adverse events per 100 patient-years (95% CI)	0.00 (0.00, 0.36)	0.00 (0.00, 2.97)	0.12 (0.01, 0.43)	0.00 (0.00, 2.86)
Maximum severity[a]				
Mild	0	0	1	0
Moderate	0	0	1	0
Severe	0	0	0	0
Maximum seriousness[b]				
Non-serious	0	0	0	0
Serious	0	0	2	0
Latest outcome[c]				

Table 19. Serious Opportunistic Infections: Frequency, Severity, Seriousness and Outcomes of Adverse Events in Clinical Trials

	Placebo-controlled UC Pool		All UC Pool	
	Etrasimod 2 mg	Placebo	Etrasimod 2 mg	Placebo
Resolved	0	0	2	0
Still present	0	0	0	0
Fatal	0	0	0	0
Unknown	0	0	0	0
Reported events (MedDRA PTs)				
Herpes simplex meningitis	0	0	1	0
Cytomegalovirus colitis	0	0	1	0

a. For the same adverse event of interest, the most severe case was selected in this summary.
b. For the same adverse event of interest, the most serious case was selected in this summary.
c. For the same adverse event of interest, the last case was selected in this summary. If last case has a missing outcome, the case is considered still present.
Table displays number of adverse events, except for the first row which displays number of patients with at least one event.
Incidence Rates: Number of subjects with events per 100 patient-years.

Placebo-controlled UC Pool includes studies: APD334-003, APD334-301, APD334-302, and APD334-308.
All UC Pool includes studies: APD334-003, APD334-005, APD334-301, APD334-302, APD334-303 (02Aug2023 Snapshot), APD334-308 and ES101002 (30Aug2022 Snapshot).
Source: Table 51a.1.5.0.1, Table 51a.2.5.0.1, Table 51a.2.6.0.1, Table 51a.2.7.0.1, Table 51a.2.5.1

The event of Herpes simplex meningitis occurred in a subject in their late 60s approximately 1 week after initiation of etrasimod 2 mg in study APD334-303. The patient had received placebo during participation in study APD334-301. Etrasimod was discontinued, the patient was treated with antiviral medication and the event resolved. The Investigator considered the event to be unlikely related to study treatment.

Cytomegalovirus colitis occurred in a 50-59 year-old female subject who received etrasimod 2 mg for approximately 1 year in study APD334-303. The subject was due for colonoscopy assessment as study protocol and had reported no symptoms that led to test for CMV. Rectum biopsy result was positive for CMV immunostain and was diagnosed with CMV colitis based on her pathological findings on colonic biopsy. Etrasimod was discontinued and the subject was treated with antiviral medication; the event resolved. The Investigator considered there was a reasonable possibility that the event was related to study treatment.

No correlation between lymphocyte counts and the frequency of opportunistic infections was observed in the clinical studies. No subjects with grade 4 lymphopenia ($<0.2 \times 10^9$/L) while on study drug subsequently had an opportunistic infection.

No case of confirmed or suspected PML has been observed in etrasimod-treated patients (All indications pool).

Post-marketing

There were no cases of serious opportunistic infections received from post-marketing sources.

SVII.3.1.4.4. Risk factors and risk groups

Patients with underlying immunodeficiency due to a comorbidity or recent or concomitant treatment with immunosuppressive drugs might be at elevated risk for opportunistic infections subsequent to treatment initiation with etrasimod.

SVII.3.1.4.5. Preventability

Suitable measures to minimise the risk and/or clinical consequences of opportunistic infections include careful patient selection (including avoidance of use of etrasimod in patients with severe active infections or active chronic infections or are in an immunodeficient state, obtaining a complete blood count prior to treatment initiation and periodically during treatment, and careful selection of patients recently or concomitantly treated with other immune-modulating or non-corticosteroid immunosuppressive therapies), vigilance for infection during and for up to 2 weeks after discontinuation of etrasimod, prompt diagnostic workup of patients with suspected infections, and effective management of patients with infections, including consideration of interrupting treatment with etrasimod in patients who develop a serious infection.

SVII.3.1.4.6. Impact on the risk-benefit balance of the product

While opportunistic infections may be fatal in rare cases, particularly in immunocompromised patients, they generally have a favourable outcome when diagnosed early and treated appropriately. In view of the low frequency of serious opportunistic infections observed in the clinical studies and with appropriate risk minimisation measures in place, the impact of this risk on the risk-benefit balance of the product is considered to be low.

SVII.3.1.4.7. Public health impact

The available data do not suggest a significantly increased drug-attributable risk for serious opportunistic infections. Consequently, the public health impact is considered to be low.

SVII.3.1.4.8. MedDRA terms

SMQ Opportunistic infections (narrow) – serious events only.

SVII.3.1.5. Important Potential Risk: Malignancy

SVII.3.1.5.1. Potential mechanisms

In view of their primary pharmacological effects, S1P receptor modulators it may be hypothesised that drugs of this class could interfere with cancer immunosurveillance, thereby increasing the risk for development or progression of malignancies. Of note, whereas etrasimod reduces the number of certain lymphocyte subpopulations in peripheral blood (e.g., peripheral blood B cells [$CD19^+$] and T cells [$CD3^+$], T-helper [$CD3^+CD4^+$], and T-cytotoxic

[$CD3^+CD8^+$] cell subsets), natural killer cells and monocytes are not affected by etrasimod. Also, T-helper cells are more sensitive to the effects of etrasimod than T-cytotoxic cells. Cancer immunosurveillance may thus be preserved.

SVII.3.1.5.2. Evidence source and strength of evidence

This potential risk is inferred from the mechanism of action of etrasimod and cases observed in clinical studies with etrasimod. Cases of malignancies (including cutaneous malignancies) have been reported in patients treated with other S1P receptor modulators.

SVII.3.1.5.3. Characterisation of the risk

Clinical Trials

The frequency, seriousness, severity and outcomes of malignancies reported in the clinical trials are summarised in Table 20 below. There were no pertinent events in the <2 mg etrasimod group.

Table 20. Malignancy: Frequency, Severity, Seriousness and Outcomes of Adverse Events in Clinical Trials

	Placebo-controlled UC Pool		All UC Pool	
	Etrasimod 2 mg	**Placebo**	**Etrasimod 2 mg**	**Placebo**
Number of patients with at least one adverse event n (%)	1 (0.2%)	0	10 (0.9%)	0
Number of adverse events n (%)	1 (0.2%)	0	11 (0.9%)	0
Incidence rate of adverse events per 100 patient-years (95% CI)	0.10 (0.00, 0.55)	0.00 (0.00, 2.97)	0.66 (0.33, 1.19)	0.00 (0.00, 2.86)
Maximum severity[a]				
Mild	0	0	4	0
Moderate	0	0	0	0
Severe	1	0	7	0
Maximum seriousness[b]				
Non-serious	0	0	5	0
Serious	1	0	6	0
Latest outcome[c]				
Resolved	1	0	5	0
Still present	0	0	5	0
Fatal	0	0	1	0
Unknown	0	0	0	0
Reported events (MedDRA PTs)				
Acute monocytic leukaemia	0	0	1	0
Bowen's disease	0	0	1	0
Breast conserving surgery	1	0	1	0
Colon cancer	0	0	1	0
Intraductal proliferative breast lesion	0	0	1	0
Large intestinal polypectomy	0	0	1	0

Table 20. Malignancy: Frequency, Severity, Seriousness and Outcomes of Adverse Events in Clinical Trials

	Placebo-controlled UC Pool		All UC Pool	
	Etrasimod 2 mg	**Placebo**	**Etrasimod 2 mg**	**Placebo**
Neuroendocrine carcinoma metastatic	0	0	1	0
Neuroendocrine tumour	0	0	1	0
Pyoderma gangrenosum[d]	0	0	1	0
Squamous cell carcinoma	0	0	2	0

a. For the same adverse event of interest, the most severe case was selected in this summary.
b. For the same adverse event of interest, the most serious case was selected in this summary.
c. For the same adverse event of interest, the last case was selected in this summary. If last case has a missing outcome, the case is considered still present.
d. Not confirmed to be malignant. The event was reported in a 40-49 year-old female subject who was receiving etrasimod 2 mg while participating in UC open label trial (APD334-303). The event was assessed as not serious and not related to study drug and the event had not resolved at the time of the report.
Table displays number of adverse events, except for the first row which displays number of patients with at least one event.
Incidence Rates: Number of subjects with events per 100 patient-years.
Placebo-controlled UC Pool includes studies: APD334-003, APD334-301, APD334-302, and APD334-308
All UC Pool includes studies: APD334-003, APD334-005, APD334-301, APD334-302, APD334-303 (02Aug2023 Snapshot), APD334-308 and ES101002 (30Aug2022 Snapshot)
Source: Table 51a.1.5.0.1, Table 51a.1.6.0.1, Table 51a.1.7.2, Table 51a.2.5.0.1, Table 51a.2.5.2, Table 51a.2.6.0.1, Table 51a.2.7.0.1, Table 51a.2.7.

Across all etrasimod clinical studies (All indications pool), one further participant with malignancy was reported: Squamous cell carcinoma of the skin was: Squamous cell carcinoma of the skin was diagnosed in a subject in their mid-60s who was receiving placebo while participating in an atopic dermatitis trial. Subsequently, 2 further manifestations of squamous cell carcinoma at other locations were reported while the patient was receiving etrasimod 2 mg. All events were reported as resolving. Another participant with pyoderma gangrenosum was reported in a 30-39 year-old female subject who was receiving etrasimod 2 mg while participating in a Crohn's disease trial. The event was assessed as not serious and not related to study drug; the dose was not changed and the event had not resolved at the time of the report.

The overall incidence rate of malignancies in the placebo-controlled UC pool (0.1 event per 100 patient-years of exposure = 100 per 100,000 person-years) is consistent with crude overall cancer incidence estimates for the 20-59 years age group published by the International Agency for Research on Cancer (IARC) for Europe (277 per 100,000 person-years) and North America (307 per 100,000 person-years).[67] Epidemiological studies in UC populations have reported a 2-fold increased risk (as compared with healthy controls) for neuroendocrine tumours (Module SI). A small (1.2-fold) increase in risk of non/melanoma skin cancer has been reported for persons with atopic dermatitis.[68]

Post-marketing

Table 21. Malignancy: Reported Events, Seriousness, and Outcomes from Post-Marketing Cases

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Neoplasm malignant	2	2	0	0	0	0	0	2
Colectomy	1	1	1	0	0	0	0	1
Total	3	3	1	0	0	0	0	3

F = fatal; H = hospitalisation; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; R = resolved/resolving; RS = resolved with sequelae; NR = not resolved; U = unknown

SVII.3.1.5.4. Risk factors and risk groups

Underlying UC is discussed as a risk factor for colorectal cancer and other malignancies (see Module SI). However, no risk factors specific to patients treated with etrasimod are known for this potential risk. If etrasimod had a causal role in the development or progression of malignancies, patients with pre-existing or active malignancies might be hypothesised to be at elevated risk for cancer progression.

SVII.3.1.5.5. Preventability

No specific preventative measures are known for this unconfirmed risk. Prompt evaluation of signs or symptoms suspicious of malignancy (e.g., suspicious skin lesions) can expedite diagnosis and might thereby help to improve the outcome of malignancies.

SVII.3.1.5.6. Impact on the risk-benefit balance of the product

If confirmed, the impact of this risk on the risk-benefit balance of the product would be determined by the magnitude of treatment-attributable risk, type of malignancy, timing of detection, and treatment options.

SVII.3.1.5.7. Public health impact

The available data do not suggest a significantly increased drug-attributable risk for malignancies in etrasimod-treated patients. Consequently, the public health impact is considered to be absent or low.

SVII.3.1.5.8. MedDRA terms

SMQ Malignancies.

SVII.3.1.6. Important Potential Risk: Serious Liver Injury

SVII.3.1.6.1. Potential mechanisms

S1P is an important mediator in the liver, regulating a variety of hepatic functions;[69] however, the mechanism by which S1P receptor modulators might cause serious liver injury is not known.

SVII.3.1.6.2. Evidence source and strength of evidence

Serious liver injury has been reported in patients treated with other S1P receptor modulators.

SVII.3.1.6.3. Characterisation of the risk

Clinical Trials

No cases with enzyme elevations meeting Hy's law criteria were reported. Two hepatic enzyme elevations were reported as SAEs from the clinical trials (All UC pool): Hepatic enzyme increased occurred in a subject in their 30s more than 6 months after initiation of etrasimod 2 mg. Additional complaints included epigastric pain and nausea. The patient was hospitalised. The hepatic event was mild, assessed as unrelated to etrasimod by the investigator, and resolved without discontinuation of study medication. Per investigator, the elevated liver enzymes were suspected to have a possible biliary aetiology.

Jaundice occurred in a subject in their 30s approximately 1 month after they withdrew consent and discontinued study treatment (placebo) due to lack of efficacy. Additional complaints included abdominal pain and nausea. The patient was hospitalised. An underlying cause was not established; however, the event was assessed as unrelated to etrasimod by the investigator, who considered it to be expected in the target population.

Post-marketing

Table 22. Serious Liver Injury: Reported Events, Seriousness, and Outcomes from Post-Marketing Cases

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Non-alcoholic steatohepatitis	1	1	0	0	0	0	0	1
Total	1	1	0	0	0	0	0	1

F = fatal; H = hospitalisation; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; R = resolved/resolving; RS = resolved with sequelae; NR = not resolved; U = unknown

SVII.3.1.6.4. Risk factors and risk groups

No specific risk factors are identified for this potential risk.

SVII.3.1.6.5. Preventability

No preventative measures are known for this potential risk. Pre-treatment assessment of hepatic enzymes is a suitable measure to identify patients with pre-existing liver disease. Monitoring of patients for development of any symptoms suggestive of hepatic dysfunction and discontinuation of treatment in patients with confirmed serious liver injury are considered adequate measures to reduce the impact of hepatotoxicity, should it occur.

SVII.3.1.6.6. Impact on the risk-benefit balance of the product

Serious drug-induced liver injury is a potentially life-threatening condition. A causal association between treatment with etrasimod and the occurrence of serious liver injury is currently unconfirmed. If confirmed, the impact of this risk on the risk-benefit balance of the product would depend on the frequency, clinical course and outcome of such events.

SVII.3.1.6.7. Public health impact

In the clinical trials, sporadic, transient elevations in liver enzymes were observed, these were generally <3× ULN and asymptomatic with no clinically meaningful trends observed. No cases with liver chemistry elevations meeting Hy's law criteria were reported. Consequently, the public health impact is currently considered to be low.

SVII.3.1.6.8. MedDRA terms

SMQ Drug related hepatic disorders - comprehensive search – serious events only.

SVII.3.1.7. Important Potential Risk: Neurological Events of PRES or Convulsion

SVII.3.1.7.1. Potential mechanisms

Neurological events including convulsions, posterior reversible encephalopathy syndrome (PRES) and atypical multiple sclerosis relapses have been rarely observed in patients treated with other S1P receptor modulators. The events were reported from multiple sclerosis populations and confounding by indication or a risk specific to patients with pre-existing cerebral disease is therefore a possibility. However, considering that PRES has also been associated with other immunomodulating agents (e.g., cyclosporine, tacrolimus) in other clinical contexts[70,71] and that S1P receptor modulators may interfere with endothelial function,[65] a potential causal association between treatment with S1P receptor modulators and an increased risk of neurological events such as PRES can be hypothesised.

SVII.3.1.7.2. Evidence source and strength of evidence

This potential risk is inferred from the mechanism of action of etrasimod and publicly available information on other S1P receptor modulators.

SVII.3.1.7.3. Characterisation of the risk

Clinical Trials

As of data lock point of this RMP, there have been no neurological events of PRES in the etrasimod clinical studies.

No relevant events were reported from the Placebo-controlled UC Pool. In the All UC Pool, there was one subject in the 2 mg etrasimod group with an AE coded to the PT Post stroke seizure [incidence rate per 100 PY (95% CI) of 0.06 (0.00, 0.33)]. The event was assessed as serious and severe; the event resolved.

Post-marketing

There were no cases of neurological events of PRES or convulsion received from post-marketing sources.

SVII.3.1.7.4. Risk factors and risk groups

No risk factors or risk groups specific to etrasimod are known. The cases of convulsion or PRES during treatment with other S1P receptor modulators were generally reported from patients participating in multiple sclerosis trials.

SVII.3.1.7.5. Preventability

Currently, no preventative measures are known. Expeditious diagnostic workup of patients with unexpected neurological symptoms such as patients with signs or symptoms suggestive of PRES, discontinuation of etrasimod in patients with suspected drug-related neurological disease, and initiation of adequate supportive treatment are considered suitable measures to minimise the risk of complications or lasting neurological sequelae.

SVII.3.1.7.6. Impact on the risk-benefit balance of the product

The impact of this potential risk on the risk-benefit balance of the product currently cannot be determined. If confirmed, the impact of this potential risk would be determined by the nature, severity, treatment options and outcomes of the neurological event as well as the magnitude of treatment-attributable risk. Patients with PRES usually recover if the cause is removed and supportive treatment is promptly initiated.[70]

SVII.3.1.7.7. Public health impact

The public health impact of this risk, if confirmed, would also depend on the nature and clinical course of the event.

SVII.3.1.7.8. MedDRA terms

PRES: PTs Autoimmune encephalopathy; Encephalopathy; Immune-mediated encephalopathy; Leukoencephalopathy; Posterior reversible encephalopathy syndrome; Toxic leukoencephalopathy.

Convulsion: PTs Alcoholic seizure; Atonic seizures; Atypical benign partial epilepsy; Clonic convulsion; Convulsions local; Convulsive threshold lowered; Drug withdrawal convulsions; Epilepsy; Epilepsy with myoclonic-atonic seizures; Faciobrachial dystonic seizure; Frontal lobe epilepsy; Hyperglycaemic seizure; Hypocalcaemic seizure; Hypoglycaemic seizure; Hyponatraemic seizure; Idiopathic generalised epilepsy; Idiopathic partial epilepsy; Myoclonic epilepsy; Partial seizures; Partial seizures with secondary generalisation; Photosensitive seizure; Post stroke epilepsy; Post stroke seizure; Post-traumatic epilepsy; Psychogenic seizure; Seizure; Seizure anoxic; Seizure cluster; Seizure like phenomena; Status epilepticus; Tonic clonic movements; Tonic convulsion.

SVII.3.2. Presentation of the Missing Information

SVII.3.2.1. Missing Information: Safety in Elderly Patients ≥65 Years of Age, Particularly with Regard to Infections, Cardiovascular Events, and Eye Affections

SVII.3.2.1.1. Evidence source

There are limited long-term safety data from elderly patients from the etrasimod clinical trials. The Placebo-controlled UC pool included 54 patients aged 65 years or older, of whom 32 patients received etrasimod. Three etrasimod-treated patients and one patient in the placebo group were ≥75 years.

There was no evidence of a higher frequency or increased severity of adverse reactions in elderly compared with younger etrasimod-treated patients. There was also no correlation between age and the effect of etrasimod on lymphocyte counts. In the population PK analysis, no clinically significant differences in the PK of etrasimod based on age were observed. However, the number of elderly patients treated with etrasimod was limited and the potential impact of the adverse events of etrasimod in this population is therefore not fully characterised and warrants further evaluation.

SVII.3.2.1.2. Anticipated risk/consequence of the missing information

The safety profile in older patients may not have been fully characterised in the clinical development program. Further evaluation involving a larger dataset could help detect risks that may occur in greater proportions in this patient population, such as infections and symptomatic bradycardia (including conduction disorders).

Module SVIII. Summary of the Safety Concerns

Table 23. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	• Macular oedema • Embryofoetal toxicity
Important potential risks	• Symptomatic bradycardia (including conduction disorders) • Serious opportunistic infections • Malignancy • Serious liver injury • Neurological events of PRES or convulsion
Missing information	• Safety in elderly patients ≥65 years of age, particularly with regard to infections, cardiovascular events, and eye affections

PART III. PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1. Routine Pharmacovigilance Activities

Routine pharmacovigilance for the lifecycle of a product is a critical component to the detection, assessment, understanding and mitigation of adverse events. Objectives of routine pharmacovigilance includes having processes in place to assure the ongoing and timely collection, processing, follow-up, and analysis of individual adverse event reports and aggregate data globally, following global safety Standard Operating Procedures and regulatory guidance.

Pfizer monitors the safety profile of its products, evaluates issues potentially impacting product benefit-risk profiles in a timely manner, and ensures that appropriate communication of relevant safety information is conveyed in a timely manner to regulatory authorities and other interested parties as appropriate and in accordance with international principles and prevailing regulations.

Routine pharmacovigilance activities beyond ADRs reporting and signal detection

Specific adverse reaction follow-up questionnaires for safety concerns:

Pregnancy follow-up questionnaires (Exposure During Pregnancy Supplemental Form for study cases and Exposure During Pregnancy Follow-up Questionnaire for non-study cases attached in Annex 4) are also utilised to collect further data on pregnancy outcome and reproductive and developmental toxicity.

III.2. Additional Pharmacovigilance Activities

The following additional pharmacovigilance activities are proposed for etrasimod:

Table 24. Summary of Etrasimod Post-Authorisation Safety Study (C5041046)

Study short name and title:	An Active Surveillance, Post-Authorization Safety Study to Characterize the Safety of Etrasimod in Patients with Ulcerative Colitis Using Real-World Data in the European Union (See Annex 3 for protocol synopsis).
Rationale and study objectives	This study will be an active safety surveillance study to assess safety events of interest that may be associated with etrasimod in the post-approval setting in the EU. The primary objective is to estimate the incidence rates of safety events of interest among patients with UC who initiate etrasimod during routine clinical care. The following are the primary safety events of interest: • Macular oedema • Symptomatic bradycardia (including conduction disorders) • Serious opportunistic infections • Malignancy • Serious liver injury • Neurological events of PRES or convulsion • Safety in elderly patients ≥65 years of age, particularly with regard to infections, cardiovascular events, and eye affections Follow-up for the primary safety events of interest will be long-term (8 years). For contextualisation and risk characterisation purposes, incidence rates will also be

Table 24. Summary of Etrasimod Post-Authorisation Safety Study (C5041046)

	estimated among the following groups: UC patients who initiate other S1P receptor modulators, and UC patients who initiate biologics with/without concurrent immunomodulators/immunosuppressants.	
Study design	Cohort study using routinely collected secondary electronic healthcare data from European database(s).	
Study population	To be eligible, patients will be required to be 16 years of age or older and diagnosed with UC.	
Milestones	**Milestone**	**Planned Date**
	Protocol draft submission	Within 6 months from approval of etrasimod by the European Commission (EC). Actual date: 25 June 2024
	Interim report submission	Within first quarter of year 5 of the study (expected 16 May 2028)
	Final study report submission	31 December 2035

Table 25. Summary of ELEVATE UC OLE (APD334-303)

Study short name and title:	An Open-Label Extension Study of Etrasimod in Subjects with Moderately to Severely Active Ulcerative Colitis (ELEVATE UC OLE; APD334-303)
Rationale and study objectives	The primary objective is to assess the safety of long-term administration of etrasimod in subjects with moderately to severely active UC. The secondary objective is to assess the long-term efficacy of etrasimod in subjects with moderately to severely active UC. Safety concerns addressed: • Macular oedema • Symptomatic bradycardia (including conduction disorders) • Serious opportunistic infections • Malignancy • Serious liver injury • Neurological events of PRES or convulsion • Embryofoetal toxicity • Safety in elderly patients ≥65 years of age, particularly with regard to infections, cardiovascular events, and eye affections
Study design	APD334-303 is an on-going, multicentre, open-label extension study in subjects with moderately to severely active UC. The study consists of: 1. An open-label treatment period (up to 5 years) and 2. Follow-up visits (2 and 4 weeks after the last administration of study treatment). All subjects will receive etrasimod 2 mg once daily for up to 5 years.

Table 25. Summary of ELEVATE UC OLE (APD334-303)

Study population	Subjects with moderately to severely active UC who previously received double-blind treatment (either etrasimod 2 mg or placebo) during participation in one of the qualified Phase 3 or Phase 2 double-blind, placebo-controlled parent studies including but not limited to: • APD334-301: Subjects who have met disease worsening criteria as defined in the inclusion criteria, after the double-blind (etrasimod or placebo) 12-Week Treatment Period, or those who complete the 52-Week Treatment Period • APD334-302: Subjects who complete the 12 weeks of double-blind (etrasimod or placebo) 12 Week Treatment Period • APD334-210: Subjects who have met disease worsening criteria as defined in the inclusion criteria, after the double-blind (etrasimod or placebo) 12-Week Treatment Period, or those who complete the 52-Week Treatment Period.	
Milestones	**Milestone**	**Planned Date**
	Final study report submission	September 2027

III.3. Summary Table of Additional Pharmacovigilance Activities

III.3.1. On-Going and Planned Additional Pharmacovigilance Activities

Table 26. On-going and Planned Additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestone	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
(Not applicable)				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
(Not applicable)				
Category 3 - Required additional pharmacovigilance activities (by the competent authority)				
An Active Surveillance, Post-Authorization Safety Study to Characterize the Safety of Etrasimod in Patients with Ulcerative Colitis Using Real-World Data in the European Union (C5041046) Planned	The primary objective is to estimate the incidence rates of safety outcomes of interest among patients with UC who initiate etrasimod during routine clinical care. Follow-up for the primary safety events of interest will be long-term (8 years). For contextualisation and risk	The following are the primary safety events of interest addressed: • Macular oedema • Symptomatic bradycardia (including conduction disorders) • Serious opportunistic infections • Malignancy • Serious liver injury	Protocol draft submission Interim report submission Final study report submission	Within 6 months from approval of etrasimod by the EC Actual date: 25 June 2024 Within first quarter of year 5 of the study (expected 16 May 2028) 31 December 2035

Table 26. On-going and Planned Additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestone	Due dates
	characterisation purposes, incidence rates will also be estimated among patients who initiate other advanced UC therapies.	• Neurological events of PRES or convulsion • Safety in elderly patients ≥65 years of age, particularly with regard to infections, cardiovascular events, and eye affections		
An Open-Label Extension Study of Etrasimod in Subjects with Moderately to Severely Active Ulcerative Colitis (ELEVATE UC OLE; APD334-303) On-going	The primary objective is to assess the safety of long-term administration of etrasimod in subjects with moderately to severely active UC. The secondary objective is to assess the long-term efficacy of etrasimod in subjects with moderately to severely active UC.	Safety concerns addressed: • Macular oedema • Symptomatic bradycardia (including conduction disorders) • Serious opportunistic infections • Malignancy • Serious liver injury • Neurological events of PRES or convulsion • Embryofoetal toxicity • Safety in elderly patients ≥65 years of age, particularly with regard to infections, cardiovascular events, and eye affections	Final study report submission	September 2027

PRES = Posterior reversible encephalopathy syndrome; UC = ulcerative colitis

PART IV. PLANS FOR POST AUTHORISATION EFFICACY STUDIES

No post-authorisation efficacy studies are planned or on-going for etrasimod.

PART V. RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

RISK MINIMISATION PLAN

V.1. Routine Risk Minimisation Measures

Table 27. Description of Routine Risk Minimisation Measures by Safety Concern

Important Identified Risks	
Macular oedema	Routine risk communication: • SmPC section 4.4 Special warnings and precautions for use • SmPC section 4.8 Undesirable effects • PL section 2 What you need to know before you take Velsipity • PL section 4 Possible side effects Routine risk minimisation activities recommending specific clinical measures to address the risk: • In SmPC section 4.4, recommendation that patients with a history of diabetes mellitus, uveitis or underlying/coexisting retinal disease undergo an ophthalmic evaluation prior to treatment initiation with etrasimod and have follow-up evaluations while receiving therapy. • In SmPC section 4.4, recommendation that patients without the risk factors above, an ophthalmic evaluation of the fundus, including the macula, is recommended within 3-4 months after starting etrasimod treatment (cases reported with etrasimod occurred within this timeframe) and at any time if there is a change in vision while taking etrasimod. • In SmPC section 4.4, recommendation to evaluate patients who present with visual symptoms of macular oedema during treatment, and to discontinue etrasimod in patients with confirmed macular oedema. Other routine risk minimisation measures beyond the Product Information: • Prescription-only medicine.
Embryofoetal toxicity	Routine risk communication: • SmPC section 4.3 Contraindications • SmPC section 4.4 Special warnings and precautions for use • SmPC section 4.6 Fertility, pregnancy and lactation • SmPC section 5.3 Preclinical safety data • PL section 2 What you need to know before you take Velsipity Routine risk minimisation activities recommending specific clinical measures to address the risk: • In SmPC sections 4.4 and 4.6, requirement for availability of a negative pregnancy test result in women of childbearing potential and counselling of such patients regarding the embryotoxicity risk before treatment initiation and that women of childbearing potential must use effective contraception during treatment and for at least 14 days after treatment discontinuation. Other routine risk minimisation measures beyond the Product Information: • Prescription-only medicine.

Table 27. Description of Routine Risk Minimisation Measures by Safety Concern

Important Potential Risks	
Symptomatic bradycardia (including conduction disorders)	Routine risk communication: • SmPC section 4.2 Posology and method of administration • SmPC section 4.3 Contraindications • SmPC section 4.4 Special warnings and precautions for use • PL section 2 What you need to know before you take Velsipity • PL section 3 How to take Velsipity Routine risk minimisation activities recommending specific clinical measures to address the risk: • In SmPC section 4.2, recommendation that etrasimod be administered with food for the first 3 days (3 doses) to attenuate potential transient heart rate lowering effects related to initiation of treatment; • In SmPC section 4.4, recommendations to obtain an ECG in all patients prior to treatment initiation to assess for pre-existing cardiac abnormalities; • In SmPC section 4.4, recommendation for first-dose monitoring for at least 4 hours for signs and symptoms of symptomatic bradycardia in patients with relevant cardiovascular comorbidities; • In SmPC section 4.4, recommendation to obtain cardiologist advice before initiation for certain patients with relevant pre-existing cardiovascular conditions; • In SmPC section 4.4, recommendation to use with caution in patients receiving treatment with a beta-blockers, calcium-channel blockers, QT prolonging medicinal products, Class Ia and Class III anti-arrhythmic substances. Other routine risk minimisation measures beyond the Product Information: • Prescription-only medicine.
Serious opportunistic infections	Routine risk communication: • SmPC section 4.3 Contraindications • SmPC section 4.4 Special warnings and precautions for use • SmPC section 4.5 Interaction with other medicinal products and other forms of interaction • PL section 2 What you need to know before you take Velsipity Routine risk minimisation activities recommending specific clinical measures to address the risk: • In SmPC section 4.4, recommendation to delay treatment initiation in patients with any active infection until the infection has resolved; • In SmPC section 4.4, recommendation to obtain a complete blood count, including lymphocyte count, prior to treatment initiation and periodically during treatment; • In SmPC section 4.4, recommendation to interrupt treatment with etrasimod in patients with a confirmed absolute lymphocyte count $<0.2 \times 10^9$/L until the level reaches $>0.5 \times 10^9$/L when re-initiation of etrasimod can be considered; • In SmPC section 4.4, recommendation to consider interruption of treatment in patients who develop a serious infection;

Table 27. Description of Routine Risk Minimisation Measures by Safety Concern

	• In SmPC section 4.4, recommendation to instruct patients to report promptly symptoms of infection to their physician; • In SmPC section 4.4, recommendation to be vigilant for clinical symptoms or unexplained neurological findings that may be suggestive of PML, to suspend treatment until PML has been ruled out, and to discontinue treatment in patients with confirmed PML; • In SmPC section 4.4, advice to consider the duration of their effects and mode of action of previously used immunosuppressive medicinal products when switching to etrasimod to avoid unintended additive immunosuppressive effects; • In SmPC sections 4.4 and 4.5, advice for caution when co-administering etrasimod and anti-neoplastic, immune-modulating or immunosuppressive (including corticosteroid) therapies to patients because of the risk of additive immune system effects during such therapy; • In SmPC sections 4.4 and 4.5, recommendation to administer any required live attenuated vaccines at least 4 weeks prior to initiation of etrasimod, and to avoid the use of live attenuated vaccines during and for at least 2 weeks after treatment with etrasimod (see SmPC section 5.1). <u>Other routine risk minimisation measures beyond the Product Information:</u> • Prescription-only medicine.
Malignancy	<u>Routine risk communication:</u> • SmPC section 4.3 Contraindications • SmPC section 4.4 Special warnings and precautions for use • SmPC section 5.3 Preclinical safety data. • PL section 2 What you need to know before you take Velsipity <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> • In SmPC section 4.4, recommendation to promptly evaluate suspicious skin lesions. <u>Other routine risk minimisation measures beyond the Product Information:</u> • Prescription-only medicine.
Serious liver injury	<u>Routine risk communication:</u> • SmPC section 4.3 Contraindications • SmPC section 4.4 Special warnings and precautions for use • PL section 2 What you need to know before you take Velsipity <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> • In SmPC section 4.4, recommendation to obtain transaminase and bilirubin levels prior to treatment initiation; • In SmPC section 4.4, recommendation to check hepatic enzymes in patients who develop symptoms suggestive of hepatic dysfunction and to discontinue treatment in case significant liver injury is confirmed.

Table 27. Description of Routine Risk Minimisation Measures by Safety Concern

	Other routine risk minimisation measures beyond the Product Information: • Prescription-only medicine.
Neurological events of PRES or convulsion	Routine risk communication: • SmPC section 4.4 Special warnings and precautions for use • PL section 2 What you need to know before you take Velsipity Routine risk minimisation activities recommending specific clinical measures to address the risk: • In SmPC section 4.4, recommendation to promptly investigate any unexpected neurological or psychiatric symptoms/signs; • In SmPC section 4.4, recommendation to discontinue etrasimod in patients with suspected PRES. Other routine risk minimisation measures beyond the Product Information: • Prescription-only medicine.
Missing Information	
Safety in elderly patients ≥65 years of age, particularly with regard to infections, cardiovascular events, and eye affections	Routine risk communication: • SmPC section 5.2 Pharmacokinetic properties • PL: not applicable Routine risk minimisation activities recommending specific clinical measures to address the risk: • None proposed. Other routine risk minimisation measures beyond the Product Information: • Prescription-only medicine.

V.2. Additional Risk Minimisation Measures

The following additional risk minimisation activities for etrasimod are summarised below:

- Healthcare Professional Checklist (Table 28)
- Patient/Caregiver Guide (Table 29)
- Pregnancy-Specific Patient Card (Table 30).

Table 28. Additional Risk Minimisation Measure: Healthcare Professional Checklist

Objectives	The objective of the healthcare professional checklist is to provide an appropriate tool to enhance awareness and knowledge of prescribers about the important potential risks and ensure optimal use of etrasimod. The healthcare professional checklist intends to remind the prescriber of the important potential risks associated with etrasimod use and the recommended tests before and during treatment. Safety concerns addressed: • Macular oedema • Symptomatic bradycardia (including conduction disorders) • Serious opportunistic infection • Malignancy • Embryofoetal toxicity • Serious liver injury • Neurological events of PRES or convulsion
Rationale for the additional risk minimisation activity	Additional awareness and knowledge of prescribers about the risks will help to mitigate these risks.
Target audience and planned distribution path	The target audience is prescribing physicians. The communication plan varies by local legal and regulatory requirements.
Plans to evaluate the effectiveness of the interventions and criteria for success	Routine pharmacovigilance activities to identify new safety signals and monitor reporting trends will be used to evaluate effectiveness.

Table 29. Additional Risk Minimisation Measure: Patient/Caregiver Guide

Objectives	The objective of the patient/caregiver guide is to provide an appropriate tool designed to enhance the awareness and knowledge of patients about the safety concerns and ensure the optimal use of etrasimod. Safety concerns addressed: • Macular oedema • Symptomatic bradycardia (including conduction disorders) • Serious opportunistic infection • Malignancy • Embryofoetal toxicity • Serious liver injury • Neurological events of PRES or convulsion
Rationale for the additional risk minimisation activity	Additional awareness and knowledge of patients about the risks will help to mitigate these risks.
Target audience and planned distribution path	The target audience is patients via their prescribing physicians. The communication plan will vary according to local legal and regulatory requirements.

Table 29. Additional Risk Minimisation Measure: Patient/Caregiver Guide

Plans to evaluate the effectiveness of the interventions and criteria for success	Routine pharmacovigilance activities to identify new safety signals and monitor reporting trends will be used to evaluate effectiveness.

Table 30. Additional Risk Minimisation Measure: Pregnancy-Specific Patient Card

Objectives	The objective of the Pregnancy Specific Patient Card is to provide an appropriate tool designed to enhance the awareness and knowledge of patients about embryofoetal toxicity in pregnant females exposed to etrasimod and ensure the optimal use of etrasimod. Safety concern addressed: • Embryofoetal toxicity.
Rationale for the additional risk minimisation activity	Additional awareness and knowledge of embryofoetal toxicity in exposed pregnant females will support the appropriate management of this risk.
Target audience and planned distribution path	The target audience is female patients of childbearing potential via their prescribing physicians. The communication plan will vary according to local legal and regulatory requirements.
Plans to evaluate the effectiveness of the interventions and criteria for success	Routine pharmacovigilance activities to identify new safety signals and monitor reporting trends will be used to evaluate effectiveness.

Removal of additional risk minimisation activities

Not applicable.

V.3. Summary of Risk Minimisation Measures

Table 31. Summary of Risk Minimisation Measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Macular oedema	Routine risk minimisation measures: • SmPC section 4.4 Special warnings and precautions for use • SmPC section 4.8 Undesirable effects • PL section 2 What you need to know before you take Velsipity • PL section 4 Possible side effects • Prescription-only medicine. Additional risk minimisation measures: • Healthcare Professional Checklist • Patient/Caregiver Guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None proposed Additional pharmacovigilance activities: • APD334-303 • Etrasimod Post-Authorisation Safety Study (C5041046)

Table 31. Summary of Risk Minimisation Measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Embryofoetal toxicity	Routine risk minimisation measures: • SmPC section 4.3 Contraindications • SmPC section 4.4 Special warnings and precautions for use • SmPC section 4.6 Fertility, pregnancy and lactation • SmPC section 5.3 Preclinical safety data • PL section 2 What you need to know before you take Velsipity • Prescription-only medicine. Additional risk minimisation measures: • Healthcare Professional Checklist • Patient/Caregiver Guide • Pregnancy-Specific Patient Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Pregnancy follow-up questionnaires to collect relevant information during follow-up activities. Additional pharmacovigilance activities: • APD334-303
Symptomatic bradycardia (including conduction disorders)	Routine risk minimisation measures: • SmPC section 4.2 Posology and method of administration • SmPC section 4.3 Contraindications • SmPC section 4.4 Special warnings and precautions for use • PL section 2 What you need to know before you take Velsipity • PL section 3 How to take Velsipity • Prescription-only medicine. Additional risk minimisation measures: • Healthcare Professional Checklist • Patient/Caregiver Guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None proposed Additional pharmacovigilance activities: • APD334-303 • Etrasimod Post-Authorisation Safety Study (C5041046)
Serious opportunistic infections	Routine risk minimisation measures: • SmPC section 4.3 Contraindications • SmPC section 4.4 Special warnings and precautions for use • SmPC section 4.5 Interaction with other medicinal products and other forms of interaction • PL section 2 What you need to know before you take Velsipity • Prescription-only medicine. Additional risk minimisation measures: • Healthcare Professional Checklist • Patient/Caregiver Guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None proposed Additional pharmacovigilance activities: • APD334-303 • Etrasimod Post-Authorisation Safety Study (C5041046)

Table 31. Summary of Risk Minimisation Measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Malignancy	Routine risk minimisation measures: • SmPC section 4.3 Contraindications • SmPC section 4.4 Special warnings and precautions for use • SmPC section 5.3 Preclinical safety data. • PL section 2 What you need to know before you take Velsipity • Prescription-only medicine. Additional risk minimisation measures: • Healthcare Professional Checklist • Patient/Caregiver Guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None proposed Additional pharmacovigilance activities: • APD334-303 • Etrasimod Post-Authorisation Safety Study (C5041046)
Serious liver injury	Routine risk minimisation measures: • SmPC section 4.3 Contraindications • SmPC section 4.4 Special warnings and precautions for use • PL section 2 What you need to know before you take Velsipity • Prescription-only medicine. Additional risk minimisation measures: • Healthcare Professional Checklist • Patient/Caregiver Guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None proposed Additional pharmacovigilance activities: • APD334-303 • Etrasimod Post-Authorisation Safety Study (C5041046)
Neurological events of PRES or convulsion	Routine risk minimisation measures: • SmPC section 4.4 • PL section 2 What you need to know before you take Velsipity • Prescription-only medicine. Additional risk minimisation measures: • Healthcare Professional Checklist • Patient/Caregiver Guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None proposed Additional pharmacovigilance activities: • APD334-303 • Etrasimod Post-Authorisation Safety Study (C5041046)
Safety in elderly patients ≥65 years of age, particularly with regard to infections, cardiovascular events, and eye affections	Routine risk minimisation measures: • SmPC section 5.2 Pharmacokinetic properties • PL: not applicable • Prescription-only medicine. Additional risk minimisation measures: • None proposed	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None proposed Additional pharmacovigilance activities: • APD334-303 • Etrasimod Post-Authorisation Safety Study (C5041046) (a safety event of interest)

PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for Velsipity (Etrasimod)

This is a summary of the risk management plan (RMP) for Velsipity. The RMP details important risks of Velsipity, how these risks can be minimised, and how more information will be obtained about Velsipity's risks and uncertainties (missing information).

Velsipity's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Velsipity should be used.

This summary of the RMP for Velsipity should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Velsipity's RMP.

I. The Medicine and What It Is Used For

Velsipity is authorised for the treatment of patients 16 years of age and older with moderately to severely active ulcerative colitis who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biological agent (see SmPC for the full indication). It contains etrasimod as the active substance and it is given orally as a film-coated tablet.

Further information about the evaluation of Velsipity's benefits can be found in Velsipity's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <link to the EPAR summary landing page>.

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Velsipity, together with measures to minimise such risks and the proposed studies for learning more about Velsipity's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Velsipity, these measures are supplemented with *additional risk minimisation* measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Velsipity is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Velsipity are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Velsipity. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

Table 32. List of Important Risks and Missing Information

Important identified risks	• Macular oedema • Embryofoetal toxicity
Important potential risks	• Symptomatic bradycardia (including conduction disorders) • Serious opportunistic infections • Malignancy • Serious liver injury • Neurological events of PRES or convulsion
Missing information	• Safety in elderly patients ≥65 years of age, particularly with regard to infections, cardiovascular events, and eye affections

II.B Summary of Important Risks and Missing Information

Table 33. Important Identified Risk: Macular Oedema

Evidence for linking the risk to the medicine	Macular oedema was observed in the etrasimod clinical trials and has been reported for other S1P receptor modulators.
Risk factors and risk groups	It has been hypothesised that patients with pre-existing impaired blood-retinal barrier function, e.g., patients with a history of diabetes mellitus, uveitis, or underlying/coexisting retinal disease, may be at elevated risk of developing macular oedema.
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.4 Special warnings and precautions for use • SmPC section 4.8 Undesirable effects • PL section 2 What you need to know before you take Velsipity • PL section 4 Possible side effects Additional risk minimisation measures: • Healthcare Professional Checklist • Patient/Caregiver Guide
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • APD334-303 • Etrasimod Post-Authorisation Safety Study (C5041046) See II.C of this summary for an overview of the post-authorisation development plan.

Table 34. Important Identified Risk: Embryofoetal Toxicity

Evidence for linking the risk to the medicine	This is inferred from non-clinical data. There are a limited amount of data from the use of etrasimod in pregnant women.
Risk factors and risk groups	Other than women of childbearing potential who are not using effective contraception, no specific risk factors or risk groups for embryofoetal toxicity subsequent to etrasimod exposure are known.
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.3 Contraindications • SmPC section 4.4 Special warnings and precautions for use • SmPC section 4.6 Fertility, pregnancy and lactation • SmPC section 5.3 Preclinical safety data • PL section 2 What you need to know before you take Velsipity Additional risk minimisation measures: • Healthcare Professional Checklist • Patient/Caregiver Guide • Pregnancy-Specific Patient Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • APD334-303 See II.C of this summary for an overview of the post-authorisation development plan.

Table 35. Important Potential Risk: Symptomatic Bradycardia (Including Conduction Disorders)

Evidence for linking the risk to the medicine	This potential risk is inferred from the mechanism of action of S1P receptor modulators and clinical study data.
Risk factors and risk groups	Patients with pre-existing cardiac conditions (e.g., patients with resting heart rate < 50 bpm, second-degree [Mobitz type I] AV block, or a history of myocardial infarction or heart failure).
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.2 Posology and method of administration • SmPC section 4.3 Contraindications • SmPC section 4.4 Special warnings and precautions for use • PL section 2 What you need to know before you take Velsipity • PL section 3 How to take Velsipity Additional risk minimisation measures: • Healthcare Professional Checklist • Patient/Caregiver Guide
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • APD334-303 • Etrasimod Post-Authorisation Safety Study (C5041046) See II.C of this summary for an overview of the post-authorisation development plan.

Table 36. Important Potential Risk: Serious Opportunistic Infections

Evidence for linking the risk to the medicine	This potential risk is inferred from the mechanism of action of etrasimod and clinical study data. The only serious opportunistic infection in an etrasimod-treated patient reported from the clinical studies was a case of herpes simplex meningitis, which rapidly resolved with antiviral treatment.
Risk factors and risk groups	Patients with underlying immunodeficiency due to a comorbidity or recent or concomitant treatment with immunosuppressive drugs might be at elevated risk for opportunistic infections subsequent to treatment initiation with etrasimod.
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.3 Contraindications • SmPC section 4.4 Special warnings and precautions for use • SmPC section 4.5 Interaction with other medicinal products and other forms of interaction • PL section 2 What you need to know before you take Velsipity Additional risk minimisation measures: • Healthcare Professional Checklist • Patient/Caregiver Guide
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • APD334-303 • Etrasimod Post-Authorisation Safety Study (C5041046) See II.C of this summary for an overview of the post-authorisation development plan.

Table 37. Important Potential Risk: Malignancy

Evidence for linking the risk to the medicine	This potential risk is inferred from the mechanism of action of etrasimod and clinical study data. Cases of malignancies (including cutaneous malignancies) have been reported in patients treated with other S1P receptor modulators. In the etrasimod clinical trials, the overall incidence of malignancies was consistent with the frequency expected in the general population.
Risk factors and risk groups	Ulcerative colitis is discussed as a risk factor for colorectal cancer and other malignancies. However, no risk factors specific to patients treated with etrasimod are known for this potential risk.
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.3 Contraindications • SmPC section 4.4 Special warnings and precautions for use • SmPC section 5.3 Preclinical safety data • PL section 2 What you need to know before you take Velsipity Additional risk minimisation measures: • Healthcare Professional Checklist • Patient/Caregiver Guide
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • APD334-303 • Etrasimod Post-Authorisation Safety Study (C5041046) See II.C of this summary for an overview of the post-authorisation development plan.

Table 38. Important Potential Risk: Serious Liver Injury

Evidence for linking the risk to the medicine	Serious liver injury is classified as an important potential risk in view of reports of such events in patients treated with other S1P receptor modulators.
Risk factors and risk groups	No specific risk factors are known for this potential risk.
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.3 Contraindications • SmPC section 4.4 Special warnings and precautions for use • PL section 2 What you need to know before you take Velsipity Additional risk minimisation measures: • Healthcare Professional Checklist • Patient/Caregiver Guide
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • APD334-303 • Etrasimod Post-Authorisation Safety Study (C5041046) See II.C of this summary for an overview of the post-authorisation development plan.

Table 39. Important Potential Risk: Neurological Events of PRES or Convulsion

Evidence for linking the risk to the medicine	This potential risk is inferred from the mechanism of action of etrasimod and publicly available information on other S1P receptor modulators.
Risk factors and risk groups	No risk factors or risk groups specific to etrasimod are known. The cases of convulsion or PRES during treatment with other S1P receptor modulators were generally reported from patients participating in multiple sclerosis trials.
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.4 Special warnings and precautions for use • PL section 2 What you need to know before you take Velsipity Additional risk minimisation measures: • Healthcare Professional Checklist • Patient/Caregiver Guide
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • APD334-303 • Etrasimod Post-Authorisation Safety Study (C5041046) See II.C of this summary for an overview of the post-authorisation development plan.

Table 40. Missing Information: Safety in Elderly Patients ≥65 Years of Age, Particularly with Regard to Infections, Cardiovascular Events, and Eye Affections

Risk minimisation measures	Routine risk minimisation measures: • SmPC section 5.2 Pharmacokinetic properties • PL: not applicable Additional risk minimisation measures: • None proposed
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • APD334-303 • Etrasimod Post-Authorisation Safety Study (C5041046) See II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-Authorisation Development Plan

II.C.1 Studies which are Conditions of the Marketing Authorisation

There are no studies that are conditions of the marketing authorisation or specific obligation of Velsipity.

II.C.2 Other Studies in Post-Authorisation Development Plan

Study short name: An Open-Label Extension Study of Etrasimod in Subjects with Moderately to Severely Active Ulcerative Colitis (ELEVATE UC OLE; APD334-303)

Purpose of the study: The primary objective is to assess the safety of long-term administration of etrasimod in subjects with moderately to severely active UC. The secondary objective is to assess the long-term efficacy of etrasimod in subjects with moderately to severely active UC. Safety concerns addressed:

- Macular oedema
- Symptomatic bradycardia (including conduction disorders)
- Serious opportunistic infections
- Malignancy
- Serious liver injury
- Neurological events of PRES or convulsion
- Embryofoetal toxicity
- Safety in elderly patients ≥65 years of age, particularly with regard to infections, cardiovascular events, and eye affections

Study short name: An Active Surveillance, Post-Authorization Safety Study to Characterize the Safety of Etrasimod in Patients with Ulcerative Colitis Using Real-World Data in the European Union (C5041046).

Purpose of the study: This study will be an active safety surveillance study to assess safety events of interest that may be associated with etrasimod in the post-approval setting in the EU.

The primary objective is to estimate the incidence rates of safety events of interest among patients with UC who initiate etrasimod during routine clinical care in the EU. The following are the primary safety events of interest:

- Macular oedema
- Symptomatic bradycardia (including conduction disorders)
- Serious opportunistic infections
- Malignancy
- Serious liver injury

- Neurological events of PRES or convulsion
- Safety in elderly patients ≥65 years of age, particularly with regard to infections, cardiovascular events, and eye affections

Follow-up for the primary safety events of interest will be long-term (8 years).

PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN

Annex 2. Tabulated Summary of Planned, On-going, and Completed Pharmacovigilance Study Program

Annex 3. Protocols for Proposed, On-going, and Completed Studies in the Pharmacovigilance Plan

Annex 4. Specific Adverse Drug Reaction Follow-up Forms

Annex 5. Protocols for Proposed and On-going Studies in RMP Part IV

Annex 6. Details of Proposed Additional Risk Minimisation Measures

Annex 7. Other Supporting Data (Including Referenced Material)

Annex 8. Summary of Changes to the Risk Management Plan Over Time

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ANNEX 4. SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Exposure During Pregnancy Follow-up Questionnaire (for non-study case)

Exposure During Pregnancy Supplemental Form (for study case)

EDP FU Questionnaire

Exposure During Pregnancy

1. According to the information provided, exposure to a product may have occurred during pregnancy or around the time of conception. Please confirm and complete all questions to the best of your ability and knowledge.

☐ Yes ☐ No ☐ Unknown

Maternal Obstetrical History

1. Occupation

_____

2. Was the mother previously pregnant?

☐ Yes ☐ No ☐ Unknown

If Yes, how many times:_____

3. Number of other children

_____

4. Outcome of previous pregnancies (e.g., live birth, miscarriage, elective termination, late fetal death, ectopic pregnancy, molar pregnancy)

_____

5. Did the mother experience previous pregnancy complications?

☐ Yes ☐ No ☐ Unknown

If yes, please specify_____

6. Did the mother experience previous fetal/neonatal abnormalities?

☐ Yes ☐ No ☐ Unknown

If yes, please specify_____

7. Does the mother have a history of sub-fertility?

☐ Yes ☐ No ☐ Unknown

If yes, please specify_____

8. Was the mother treated for infertility?
☐ Yes ☐ No ☐ Unknown

If yes, please specify_____

9. Mother's Relevant History (i.e., risk factors including environmental or occupational exposures (e.g., AIDS, toxins)).

10. Does the mother have a family history of congenital abnormality/ genetic diseases, and/or consanguinity (or any family relation or lineage) between parents?
☐ Yes ☐ No ☐ Unknown

If yes, please specify_____

11. Results of serology tests (e.g., rubella, toxoplasmosis, etc.)

Maternal Information

1. Ante-natal check-up (e.g., fetal ultrasound, serum markers, etc.). Please specify dates in dd-Mmm-YYYY format and check-up results for this pregnancy.
_____

2. First day of last menstrual period (dd-Mmm-yyyy)
_____

3. Number of fetuses for this pregnancy
_____

4. Estimated delivery date for this pregnancy (dd-Mmm-yyyy)
_____

5. Gestational period at time of initial suspect drug exposure

_____ ☐ Trimester ☐ Month

6. Did the mother smoke during this pregnancy?

☐ Yes ☐ No ☐ Unknown

If Yes, frequency:_____

7. Did the mother drink alcohol during this pregnancy?

☐ Yes ☐ No ☐ Unknown

If Yes, frequency:_____

8. Did the mother use illicit drugs during this pregnancy?

☐ Yes ☐ No ☐ Unknown

If Yes, frequency:_____

9. Did the mother experience any problems before delivery?

☐ Yes ☐ No ☐ Unknown

If yes, please specify_____

10. Did the mother experience any problems during delivery (including delivery complications, fetal distress, amniotic fluid abnormal, abnormal placenta)?

☐ Yes ☐ No ☐ Unknown

If yes, please specify_____

11. Did the mother experience any problems after delivery?

☐ Yes ☐ No ☐ Unknown

If yes, please specify_____

12. Mode of delivery

☐ Vaginal ☐ Cesarean ☐ Unknown

13. Outcome of this pregnancy

- ☐ Full term live birth
- ☐ Premature live birth
- ☐ Post-mature live birth
- ☐ Stillbirth
- ☐ Late foetal death
- ☐ Ectopic pregnancy
- ☐ Molar pregnancy
- ☐ Spontaneous abortion/miscarriage
- ☐ Induced/elective abortion
- ☐ Unknown

14. Date of outcome of this pregnancy (dd-Mmm-yyyy)

_____

Neonatal Information

1. Sex (at birth)

☐ Male ☐ Female

2. Weight at birth (number and unit)

_____ ☐ kg ☐ lbs & oz

3. Length at birth (number and unit)

_____

4. Head circumference at birth (number and unit)

_____

5. Apgar score at 1 min

_____

6. Apgar score at 5 min

_____

7. Gestational age at birth in weeks

_____

8. Outcome of Fetus/Infant

☐ Healthy newborn
☐ Congenital malformation/anomaly (specify below)
☐ Other neonatal problem/abnormality (include dysmaturity, neonatal illness, hospitalization, drug therapies) (specify below)
☐ Intrauterine death
☐ Neonatal death
☐ Outcome pending (not born yet)
☐ Perinatal complications (specify below)
☐ Post-perinatal complications (specify below)
☐ Unknown

Please specify:

Paternal Information

1. Father's Age

_____ ☐ Years ☐ Months ☐ Days

Age Group:

☐ Adolescent (12-17 Years) ☐ Adult (18-64 Years) ☐ Elderly (65 or older)

2. Occupation

_____

3. Father's Relevant History (i.e., risk factors including environmental or occupational exposures (e.g., AIDS, toxins)).

4. Were any drugs (e.g., over-the-counter, medical prescription) taken by the father during the mother's pregnancy or around the time of conception?

☐ Yes ☐ No ☐ Unknown

If yes, please specify:_____

5. Did the father smoke during the mother's pregnancy or around the time of conception?

☐ Yes ☐ No ☐ Unknown

If Yes, frequency:_____

6. Did the father drink alcohol during the mother's pregnancy or around the time of conception?

☐ Yes ☐ No ☐ Unknown

If Yes, frequency:_____

7. Did the father use illicit drugs during the mother's pregnancy or around the time of conception?

☐ Yes ☐ No ☐ Unknown

If Yes, frequency:_____

8. Does the father have a family history of congenital abnormality/ genetic diseases, and/or consanguinity (or any family relation or lineage) between parents?

☐ Yes ☐ No ☐ Unknown

If yes, please specify:_____

Exposure During Pregnancy (EDP) Supplemental Form

AER # (*insert when known*)

Local #	Date Reported to Pfizer

PROTOCOL # **SUBJECT #**

Complete whenever an embryo or fetus has been exposed to study drug. Send as soon as EDP has been diagnosed, together with the SAE Report Form with the appropriate fields completed. If more space is needed, use additional copies of this page.

Pregnancy

First Day of Last Menstrual Period (DD-MMM-YYYY)

Estimated Date of Delivery (DD-MMM-YYYY)

Number of Foetuses

Gestation at time of initial exposure weeks **Or, if number of weeks unknown:** ☐ First trimester? ☐ Second trimester? ☐ Third trimester?

Relevant History/Exposure to Products

Risk factors for adverse pregnancy outcomes including environmental or occupational exposures, medical disorder e.g. hypertension, diabetes, seizure disorder, thyroid disorder, asthma, allergic disease, heart disease, psychiatric or mental health disorders, sexual transmitted disorders, hepatitis, AIDS, and other predisposing factors for neurodevelopmental disorders. Any treatment for infertility (please specify).Family history of congenital abnormality/genetic diseases, consanguinity (or any family relation or lineage) between parents (specify degree):

1) Did the mother smoke during this pregnancy? ☐ No ☐ Yes: Number per day?

2) Did the mother drink alcohol during this pregnancy? ☐ No ☐ Yes : Frequency?

3) Did the mother use illicit drugs during this pregnancy? ☐ No ☐ Yes : Frequency?

Obstetrical History *(Check the box if not applicable)*

☐ Not Applicable: No previous pregnancy

Number of previous pregnancies Number of other children

Outcome of previous pregnancies (live birth, miscarriage, elective termination with specification of gestational length and context, late fetal death, ectopic pregnancy, molar pregnancy).

Previous maternal pregnancy complications. Previous fetal/neonatal abnormalities and type. History of sub-fertility.

OUTCOME OF PREGNANCY

Complete and send after the end of pregnancy in all cases when an embryo or fetus has been exposed to study drug

Date of outcome of pregnancy DD-MMM-YYYY

Mode of delivery (e.g., natural birth [i.e., vaginal delivery without medication or anesthesia], cesarean section): [ ]

Pregnancy outcome

Check one ☐ Full term live birth ☐ Preterm live birth ☐ Stillbirth* ☐ Spontaneous abortion/miscarriage* ☐ Induced abortion ☐ Unknown

Gestational age at birth in weeks, (if known):

Complete also the Serious Adverse Event section of the report

Infant

Check one ☐ Normal ☐ Congenital Malformation/Anomaly** ☐ Other neonatal problem** ☐ Unknown

Other neonatal problem/abnormality (include dysmaturity, neonatal illness, foetal distress, amniotic fluid abnormal, anormal placenta hospitalization, drug therapies) Specify:

Apgar Score 1min 5min

☐ Male ☐ Female Birthweight grams ***Or, if birthweight in grams unknown:*** Birthweight ☐ lb ☐ oz

Length at birth: ☐ in ☐ cm Head Circumference at birth: ☐ in ☐ cm

****Complete also the Serious Adverse Event section of the report, specifying the diagnosis as the Serious Adverse Event***

Exposure During Pregnancy (EDP) Supplemental Form

AER # (*insert when known*)											

Local #	Date Reported to Pfizer

PROTOCOL # **SUBJECT #**

Paternal Information *(Check the box if not applicable)*

☐ Not Applicable

Date of Birth (dd-Mmm-yyyy) : or **Occupation**

Age (years): or

Age group (e.g., adult):

Relevant History

Risk factors including environmental or occupational exposures, e.g. AIDS, toxins. Family history of congenital abnormality/genetic diseases, consanguinity (or any family relation or lineage) between parents (specify degree):

Exposure to Products

Where any drugs (e.g., OTC, medical prescription) taken by the father during the mother's pregnancy? ☐ No ☐ Yes, *please specify*

Product	Indication	Start Date \ Stop Date	Reason for stopping	Dose	Formulation	Frequency
		DD-MMM-YYYY DD-MMM-YYYY				
		DD-MMM-YYYY DD-MMM-YYYY				
		DD-MMM-YYYY DD-MMM-YYYY				
		DD-MMM-YYYY DD-MMM-YYYY				

Exposure to Products - Recreational Drug Use

1) Did the father smoke during the mother's pregnancy? ☐ No ☐ Yes: Number per day?

2) Did the father drink alcohol during the mother's pregnancy? ☐ No ☐ Yes : Frequency?

3) Did the father use illicit drugs during the mother's pregnancy? ☐ No ☐ Yes : Frequency?

ANNEX 6. DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Draft key messages of the additional risk minimisation measures

Prior to the launch of etrasimod in each Member State, the MAH must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The main objective of the programme is to increase awareness about the important identified and potential risks of the medicinal product, specifically in regard to macular oedema, symptomatic bradycardia (including conduction disorders), serious opportunistic infections, malignancy, embryofoetal toxicity, serious liver injury, and neurological events of PRES or convulsion.

The MAH shall ensure that in each Member State where etrasimod is marketed, all healthcare professionals who are expected to prescribe have access to/are provided with the following educational package:

- Healthcare Professional Checklist
- Patient/Caregiver Guide
- Pregnancy-Specific Patient Card.

Healthcare Professional Checklist

The Healthcare Professional Checklist shall contain the following key messages:

Before first dose

Lists of tests and checks to be conducted prior to treatment initiation with etrasimod:

- An electrocardiogram (ECG) should be obtained in all patients to assess for pre-existing cardiac abnormalities.
- Etrasimod should not be used in patients:
    - who in the last 6 months experienced myocardial infarction, unstable angina pectoris, stroke, transient ischaemic attack (TIA), decompensated heart failure requiring hospitalisation, or New York Heart Association (NYHA) Class III/IV heart failure.

- with history or presence of Mobitz type II second-degree or third-degree atrioventricular (AV) block, sick sinus syndrome, or sino-atrial block, unless patient has a functioning pacemaker.

- Cardiologist advice should be obtained in patients with symptomatic bradycardia and other pre-existing cardiac conditions, to determine overall benefit risk and the most appropriate monitoring strategy.

- Caution should be taken when initiating etrasimod in patients taking medicines known to decrease heart rate.

- Etrasimod should not be used in patients with any active infection or live attenuated vaccine immunisations within the last 4 weeks.

- A recent complete blood count (CBC), including lymphocyte count, should be obtained.

    - Etrasimod should not be used in patients with an absolute lymphocyte counts $< 0.2 \times 10^9$/L.

- Recent transaminase and bilirubin levels should be available.

    - Etrasimod must not be used in patients with severe hepatic impairment.

- In women of childbearing potential, a pregnancy test must be negative and patients must be counselled on risk for the foetus. Provide a pregnancy-specific patient card to all female patients of childbearing potential.

    - Etrasimod must not be used during pregnancy or in women of childbearing potential not using effective contraception.

- It is recommended that patients with history of diabetes mellitus, uveitis, and/or underlying/co-existing retinal disease, who are at increased risk of developing macular oedema, undergo an ophthalmic evaluation prior to treatment initiation.

    - Patients with macular oedema should not use etrasimod.

Monitoring activities during and after treatment

- In patients with resting heart rate < 50 bpm, second-degree AV block [Mobitz type I], or a history of myocardial infarction or heart failure, monitoring is recommended after the first dose:

    - 4-hour monitoring for signs and symptoms of symptomatic bradycardia (including dizziness), and hourly pulse and blood pressure. An ECG prior to and at the end of this 4-hour period is recommended.

- Additional monitoring is recommended in patients, if at the end of 4-hour period:
    - Heart rate is < 45 bpm.
    - Heart rate is the lowest value post dose, suggesting that the maximum decrease in heart rate may not have occurred yet.
    - ECG shows evidence of a new onset second-degree or higher AV block.
    - QTc interval is ≥ 500 msec.
- Recommendation for measuring blood pressure regularly while on treatment.
- When reinitiating treatment after an interruption of 7 or more consecutive days, consideration may be given to repeating the baseline ECG and/or monitoring depending on the results of the first evaluation, change in patient characteristics, and duration of interruption.
- Recommendation for assessments of CBC periodically during treatment.
- Treatment interruption if a patient develops a serious infection.
- Physicians should be vigilant for clinical symptoms or unexplained neurologic findings that may be suggestive of PML. If PML is suspected, treatment with etrasimod should be suspended until PML has been excluded by an appropriate diagnostic evaluation.
- Caution should be used when co-administering etrasimod and anti-neoplastic, immune-modulating, or immunosuppressive (including corticosteroid) therapies to patients, because of the risk of additive immune system effects during such therapy.
- The use of live attenuated vaccine should be avoided for at least 2 weeks after discontinuation of treatment with etrasimod.
- Hepatic enzymes should be monitored at months 1, 3, 6, 9, and 12 on therapy and periodically thereafter. Etrasimod should be discontinued if significant liver injury is confirmed.
- Women of childbearing potential should use effective contraception to avoid pregnancy during treatment and for at least 14 days after stopping etrasimod. Pregnancy testing should be repeated regularly. If a woman becomes pregnant during treatment, etrasimod must be immediately discontinued.
- Patients with a history of diabetes mellitus, uveitis, and/or an underlying/co-existing retinal disease should undergo an ophthalmic evaluation **regularly**. An ophthalmic evaluation should be made in patients developing a change in vision.

- In patients without risk factors for macular oedema (such as history of diabetes mellitus, uveitis, and/or retinal disease), an ophthalmic evaluation of the fundus, including the macula, is recommended within 3-4 months after starting etrasimod treatment (cases reported with etrasimod occurred within this timeframe) and at any time while on treatment if there is a change in vision.

- Patients should be cautioned against exposure to sunlight without protection to prevent the development of cutaneous malignancies. Patients should not receive concomitant phototherapy with UV-B-radiation or PUVA-photochemotherapy.

- Patients should be counselled for symptoms of PRES. A complete physical and neurological examination should be done and an MRI considered for patients who develop unexpected neurological or psychiatric symptoms/signs or any symptoms suggestive of an increase of intracranial pressure, or accelerated neurological deterioration. Treatment with etrasimod should be discontinued if PRES is suspected.

Patient/Caregiver Guide

The Patient/Caregiver Guide shall contain the following key messages:

- Etrasimod should not be used in patients with myocardial infarction, unstable angina pectoris, stroke, TIA, decompensated heart failure requiring hospitalisation, or NYHA Class III/IV heart failure in the last 6 months or with a history or presence of Mobitz type II second-degree or third-degree AV block, sick sinus syndrome, or sino-atrial block, unless the patient has a functioning pacemaker.

- Patients should have a baseline ECG prior to receiving the first dose.

- For patients with certain heart conditions, heart rate should be monitored for 4 hours after the first dose of etrasimod, for signs and symptoms of symptomatic bradycardia (including dizziness), including hourly pulse and blood pressure checks. An ECG before and after the 4 hours should also be performed for these patients.

- Patients should inform their prescriber if etrasimod treatment is interrupted for 7 or more consecutive days, since a new examination of the heart may be necessary before starting the treatment again.

- Information to report immediately: symptoms indicating low heart rate (such as dizziness, vertigo, nausea, or palpitations) when starting etrasimod. Caution should be taken with concomitant use of medicines that slow the heart rate. Patients should tell any doctor they see that they are being treated with etrasimod.

- Description of signs/symptoms of infections the patient needs to be aware of, during and after treatment, so that they can seek attention from their HCP.

- Description of signs/symptoms of serious liver injury that the patient needs to be aware of, including unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine.

- Etrasimod must not be used during pregnancy or in women of childbearing potential not using effective contraception.

    - Women of childbearing potential must use effective contraception during and for at least 14 days after discontinuation of treatment.

    - Women of childbearing potential must have a negative pregnancy test before treatment initiation with etrasimod. Patients should tell their doctors straight away if they become pregnant while taking etrasimod. Pregnancy testing should be repeated regularly.

- Description of risk factors and signs/symptoms of macular oedema and the need to seek medical attention if symptoms develop.

- Be informed to notify their doctor if suspicious skin lesions are observed and to limit their exposure to sun light and UV (ultraviolet) light, by wearing protective clothing and applying regular sunscreen (with high sun protection factor).

- Description of signs/symptoms of PRES and PML the patient needs to be aware of, including developing severe headache, feel confused, or have seizures and loss of vision.

Pregnancy-Specific Patient Card

The pregnancy-specific patient card (for women of childbearing potential) shall contain the following key messages:

- Etrasimod is contraindicated during pregnancy and in women of childbearing potential not using effective contraception due to its embryotoxic potential.

- Women of childbearing potential must have a negative pregnancy test before treatment initiation, use effective contraception during treatment and for at least 14 days after treatment discontinuation.

- Pregnancy testing should be repeated regularly.

- If a woman becomes pregnant while on treatment, etrasimod must be immediately discontinued and follow up examinations should be performed.