14 December 2023
EMA/6733/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Velsipity

International non-proprietary name: Etrasimod

Procedure No. EMEA/H/C/006007/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation	Explanation
5-ASA	5-aminosalicyclic acid
AA	Alopecia areata
AAS	Atomic absorption spectrometry
AD	Atopic dermatitis
ADME	Absorption, distribution, metabolism, and excretion
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ALC	Absolute lymphocyte count
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
$AUC_{0-\infty}$	Area under the concentration-time curve from time 0 to infinity
AUC_{0-24}	Area under the concentration-time curve from time 0 to 24 hours
AUC_{0-last}	Area under the concentration-time curve from time 0 to time of last measured concentration
AV	Atrioventricular
BCS	Biopharmaceutics classification system
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
BP	Blood pressure
bpm	Beats per minute
CBC	Complete blood count
CD#	Cluster of differentiation # (e.g., CD3, CD4, CD5, CD6, CD8)
CFT	Central foveal thickness
cGMP	Current good manufacturing practice
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
C_{max}	Maximum plasma concentration
CMH	Cochran-Mantel-Haenszel
CMS	Concerned member state

Abbreviation	Explanation
CNS	Central nervous system
CO	Clinical overview
CoA	Certificate of analysis
COVID-19	Coronavirus disease 2019
C-QTc	Concentration-QT-corrected
CRP	C reactive protein
CRS	Chemical Reference Substance (official standard)
CSR	Clinical study report
CV	Coefficient of variation
CXCR3	Chemokine C-X-C motif receptor 3
CYP	Cytochrome P450
DDI	Drug-drug interaction
DLCO	Diffusing capacity of lung carbon monoxide
DSC	Differential scanning calorimetry
DVS	Dynamic vapour sorption
EAIR	Exposure-adjusted incidence rate
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EOE	Eosinophilic oesophagitis
ES	Endoscopic subscore
EU	European Union
FAS	Full analysis set
FDA	United States Food and Drug Administration
FD&C	Federal Food, Drug and Cosmetic
FEV_1	Forced expiratory volume in 1 second
FTIR	Fourrier transform infrared spectroscopy
FOXP3	Forkhead box P3
FVC	Forced vital capacity
GC	Gas chromatography
GCP	Good clinical practice

Abbreviation	Explanation
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GIRK	G protein-gated inwardly rectifying potassium
HALMED	Agencija za lijekove i medicinske proizvode
HDPE	High density polyethylene
HPLC	High performance liquid chromatography
HR	Heart rate
HSGC	Head space gas chromatography
IBD	Inflammatory bowel disease
IBDQ	Inflammatory bowel disease questionnaire
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IPC	In-process control
IL-17	Interleukin-17
IL17A	Interleukin 17A protein
IR	Immediate-release/infrared
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
IU	International units
JAK	Janus kinase
KF	Karl Fischer
LC MS/MS	Liquid chromatography-tandem mass spectrometry
LDPE	Low density polyethylene
LS	Least square
M3	Metabolite AR503641
M6	Metabolite AR504344
MAA	Marketing authorisation application
MAH	Marketing authorisation holder
MMS	Modified mayo score
MO	Major objection
MRI	Magnetic resonance imaging
MS	Multiple sclerosis/mass spectrometry

Abbreviation	Explanation
ND	Not detected
NDA	New drug application
NK	Natural killer
NLT	Not less than
NMR	Nuclear magnetic resonance
NMT	Not more than
NOR	Normal operating range
NRI	Nonresponder imputation
NRS	Numeric rating score
NT	Not tested
NYHA	New York Heart Association
OCT	Optical coherence tomography
OLE	Open-label extension
OOS	Out of specification
OSM	Oncostatin-M
PAR	Proven acceptable range
PAS	Pooled analysis set
PASS	Post-authorisation safety study
PD	Pharmacodynamics
PDE	Permitted daily exposure
PE	Polyethylene
PFT	Pulmonary function test
Ph. Eur.	European Pharmacopoeia
PIL	Patient information leaflet
PK	Pharmacokinetic
PML	Progressive multifocal leukoencephalopathy
PP	Polypropylene
PPQ	Process performance qualification
PRES	Posterior reversible encephalopathy syndrome
PT	Preferred term
PV	Pharmacovigilance
PVC	Polyvinyl chloride

Abbreviation	Explanation
QC	Quality control
RB	Rectal bleeding
RH	Relative humidity
RMS	Reference member state
RRT	Relative retention time
RSD	Relative standard deviation
S1P	Sphingosine 1-phosphate
$S1P_{1,4,5}$	Sphingosine 1-phosphate receptors 1, 4, and 5
SAE	Serious adverse event
SAP	Statistical analysis plan
SAWP	Scientific advice working party
SCE	Summary of clinical efficacy
SCS	Summary of clinical safety
SCXRD	Single crystal x-ray data
SD	Standard deviation
SDEI	Sponsor-designated event of interest
SF	Stool frequency
SF-36	Medical outcomes study 36-item short form health survey
SIP	Sterilisation in place
SmPC	Summary of product characteristics
SMQ	Standardised MedDRA queries
SOC	System organ class
STRIDE-II	Selecting Therapeutic Targets in Inflammatory Bowel Disease-II
TBNK	T cells, B cells, and natural killer cells
TEAE	Treatment-emergent adverse event
Th2	T helper type 2
Th17	T helper type 17
t_{max}	Time to maximum plasma concentration
TNFα	Tumour necrosis factor alpha
TNF	Tumour necrosis factor
TNFRSF9	Tumour necrosis factor receptor subfamily 9
TTC	Threshold of toxicological concern

Abbreviation	Explanation
UC	Ulcerative colitis
ULN	Upper limit of normal
UGT	Uridine 5’-diphospho-glucuronysltransferase
US	United States
UV	Ultraviolet
WPAI-UC	Work Productivity and Activity Impairment Questionnaire - Ulcerative Colitis
WRO	Written response only
XRD	X-ray diffraction
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Pfizer Europe MA EEIG submitted on 11 November 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Velsipity, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 31 October 2022

The applicant applied for the following indication:

Velsipity is indicated for the treatment of patients 16 years of age and older with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or an advanced treatment.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision EMEA-C2-002713-PIP01-19-M02 the agreement of a paediatric investigation plan (PIP)

At the time of submission of the application, the PIP P/0409/2022 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.4.2. New active substance status

The applicant requested the active substance etrasimod contained in the above medicinal product to be considered as a new active substance, as the applicant claimed that it is not a constituent of a medicinal product previously authorised within the European Union.

1.5. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	**Reference**	**SAWP co-ordinators**
27 June 2019	EMEA/CHMP/SAWP/340666/2019 EMEA/H/SA/4131/1/2019/SME/HTA/II	*Livia Puljak, Minne Casteels*

The scientific advice pertained to the following *clinical* aspects:

The overall clinical development program in particular the drug-drug interaction study, safety assessment, overall design of the phase III trials, definition of patient populations, choice of endpoints, choice of comparator and additional HTA-relevant issues.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Martina Weise Co-Rapporteur: Margareta Bego

The application was received by the EMA on	11 November 2022
The procedure started on	1 December 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	28 February 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	6 March 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	30 March 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	11 August 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	22 September 2023
The CHMP Rapporteurs circulated the updated CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	22 September 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	28 September 2023
The CHMP Rapporteurs circulated the updated CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	06 October 2023
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	12 October 2023

The applicant submitted the responses to the CHMP List of Outstanding Issues on	13 November 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	01 December 2023
The CHMP Rapporteurs circulated the updated CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	08 December 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Velsipity on	14 December 2023
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product	14 December 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Ulcerative colitis (UC) is a chronic gastrointestinal inflammatory disorder that involves the surface mucosa, the crypt epithelium, and the submucosa of the colon. Patients with UC suffer from diarrhoea, rectal bleeding, weight loss, abdominal pain, fever, and an increased risk of colorectal cancer, which can have a profound impact on patients' quality of life.

The pathology of UC is characterised by a life-long chronic course of remissions and exacerbations. Until a cure is found, the overall goal of treatment for patients with active UC is to induce and maintain remission and to induce and maintain mucosal healing. Despite the advancements in therapies available to patients with UC, there are still a significant number of patients with moderate to severe UC who do not respond, lose response or are intolerant to available therapies. There is a high unmet need for new efficacious treatments for patients with manageable safety and with the convenience of an oral administration.

2.1.2. Epidemiology

UC's prevalence is estimated to be 70-500 cases per 100.000 with peak age of onset between 15 and 25 years. Within Europe there is an east-west and north-south gradient, but the incidence appears to have increased in southern and eastern countries during recent years (ECCO guideline, 2017). In 15% of cases, UC is diagnosed in childhood and may present before school age. In general, mortality is not increased in UC, but the disease may present as life-threatening acute severe colitis. Patients may live with a considerable symptom burden and high risk of disability despite medical treatment. While the incidence is increasing in recent years, partly as a consequence of aging, but partly as a consequence of late manifestation, the mean age of patients suffering from UC appears to be increasing.

2.1.3. Biologic features, aetiology and pathogenesis

UC is a chronic, relapsing inflammatory bowel disease affecting the rectum and sigmoid and, in many instances, also other parts of, or the entire colon. The aetiology of UC is multifactorial, but likely includes a dysregulated mucosal immune response against commensal non-pathogenic bacteria of the colon, resulting in bowel inflammation.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Onset of disease most commonly occurs between 15 and 40 years of age. The clinical course of UC is characterised by a lifelong course of remissions and exacerbations. Patients with UC suffer from recurrent episodes of diarrhoea, rectal bleeding, weight loss, abdominal pain, fever, and are at an increased risk of perforated bowel, and toxic megacolon, and colorectal cancer. The estimated risk of colorectal cancer is approximately 2% after 10 years, 5% to 10% after 20 years, and 12% to 30% after 30 to 35 years of UC. Patients have a 10% cumulative risk of colectomy 5 years after diagnosis, and 15% at 10 years. However, with colectomy, there is a 50% risk of continued inflammation in the residual intestinal pouch (pouchitis). After 10 years, approximately 12% of patients experience pouch failure and require conversion to a permanent ileostomy. Surgical complications of proctocolectomy with ileostomy include stenosis, prolapse, and other abdominal/pelvic sequelae including small bowel obstruction, fistula, infection, persistent pain, unhealed perineal wound, sexual and bladder dysfunction, and infertility.

Patients with UC may also experience extra-intestinal manifestations including primary sclerosing cholangitis or eye, joint, or skin manifestations. Improved intestinal disease activity in UC is associated with an improvement in some extra-intestinal manifestations.

2.1.5. Management

The mainstay of therapy for mild to moderate UC is the treatment with 5-aminosalicylic (5-ASA) agents. These agents are effective at inducing and maintaining remission in UC. The majority of patients with moderate to severe active UC benefit from topical, oral or parenteral glucocorticosteroids. Remission, however, cannot be maintained with steroids due to its well-known adverse effects. Azathioprine (AZA) or mercaptopurine (MP) has been employed as glucocorticoid-sparing agents in patients unable to be weaned from glucocorticoids. Anti-tumour necrosis factor α (TNF) agents (infliximab, adalimumab and golimumab), integrin inhibitors (vedolizumab), IL-12/IL-23 inhibitors (ustekinumab) and novel immunomodulatory agents (JAK-inhibitors such as tofacitinib, filgotinib and upadacitinib) are indicated for the treatment of UC patients refractory to standard treatment (as previously described). One S1P modulator is also licensed for the moderate to severe UC indication not responsive to standard treatments (ozanimod). The biologic anti-TNF agents were the first newer-generation drugs to be approved for the treatment of UC, offering a treatment option for patients who had failed "conventional therapy" (the AZA and MP immunosuppressants). In a systematic review of clinical trials, a high proportion of patients treated with anti-TNF therapy, however, fail to achieve an initial response or remission to therapy. Within reported clinical trials, approximately 19% to 58% of patients are primary non-responders (i.e., fail to achieve clinical response) to anti-TNF therapy. Gordon et al, 2015 also reported that between 17% to 22% of patients with UC experienced a secondary nonresponse (i.e., loss of response after initial response). Since none of the mentioned other treatments has shown overwhelmingly superior response- or remission rates in the clinical trials, similar assumptions can be made for the other substances.

Real world evidence supports that many patients with UC treated with biologic therapy frequently require dose increases or need to switch therapies in order to improve disease control. Using a

database of chart information abstracted by selected gastroenterologists across the US and 5 European Union (EU) countries (France, Germany, Italy, Spain and the United Kingdom [UK]), treatment patterns of patients with moderate to severe UC with documented administration of biologic agents were examined (Armuzzi, 2020). Among patients using biologic therapy for greater than 3 months, the dose administered was greater than the indicated dose or dose frequency (in the US: 37% for infliximab, 13% for adalimumab, 25% for vedolizumab). In this study, switching therapy was common. For the whole sample size (N = 1419), 69% of patients were on their second line of therapy and 34% were on their third line of therapy. Biologic agents were the most common second line (40%) and third-line therapies (57%). The primary reason (> 80%) for switching therapy was efficacy-related (e.g., primary or secondary nonresponse).

Safety concerns related to using anti-TNF agents include serious infections leading to hospitalisation or death, including tuberculosis, bacterial sepsis, invasive fungal infections, and infections due to opportunistic pathogens. Ustekinumab, which inhibits the IL-12/23 p40 subunit, is, like the anti-TNFs, also susceptible to loss of response due to anti-drug antibodies (ADAs) and is associated with serious and opportunistic infections (including reactivation of latent tuberculosis), malignancies, and skin cancers. Serious hypersensitivity reactions have also been reported. Vedolizumab is associated with safety concerns including injection-related reactions and hypersensitivity, infections including tuberculosis and progressive multifocal leukoencephalopathy (PML), and malignancies. Tofacitinib, filgotinib and upadacitinib are the oral immunomodulators approved for moderate to severe UC. While the oral route of administration advanced the treatment for patients with moderate to severe UC, both substances associated with greater risk of serious infections, opportunistic infections and herpes zoster infections (including meningoencephalitis, ophthalmologic, and disseminated cutaneous infections). In the EU, all JAK inhibitors are to be used with caution in patients with known risk factors for venous thromboembolism (VTE), including prior VTE, major surgery, immobilisation, myocardial infarction within the previous 3 months, heart failure, combined hormonal contraceptives or hormone replacement therapy, inherited coagulation disorder, or malignancy. Additional VTE risk factors such as age, obesity, diabetes, hypertension, and smoking status should be considered.

Surgery with colectomy is curative but can be associated with significant morbidity and is thus reserved for acute severe (fulminant) colitis or resistant cases and in some cases as cancer treatment or prevention. Intestinal continuity can be restored by construction of an ileo-anal pouch.

According to the CHMP UC guideline (2018), the goal of treatment of ulcerative colitis is achieving and maintaining symptomatic and endoscopic remission. However, in recent years a slightly different approach has been emerged which was termed “treat to target” (Peyrin-Biroulet 2015; Turner 2021). This lists targets divided into those with immediate and short term timeframes, those with intermediate time-frame, and those with long-term time-frame. While “clinical response” and “clinical remission” are coded as immediate and medium-term targets, the endoscopic healing and absence of disability and normalised health-related quality of life are classified as long-term targets.

2.2. About the product

Etrasimod is a S1P modulator with selective activity at S1P1, 4, 5. Etrasimod partially and reversibly sequesters specific lymphocyte subsets in lymph nodes, resulting in a reduction of activated lymphocytes in the tissue. Critical components of innate immune function are maintained including no notable impact on the number of circulating NK cells or monocytes.

Upon binding to S1P1, synthetic receptor modulators have been observed to act as functional antagonists through the β-arrestin pathway by inducing and sustaining receptor internalisation. Loss of cell surface expressed S1P1 (typically on B and T lymphocytes) prevents cells from migrating down S1P receptor gradients and results in lymphocyte retention within lymphoid tissue. This lymphocyte

retention in lymphoid tissue subsequently lowers the amount of peripheral blood lymphocytes available to be recruited to sites of inflammation. Lowering of peripheral blood lymphocytes via functional antagonism of S1P1 has been shown to reduce inflammation and induce clinical remission in multiple sclerosis as well as UC. A reduction in infiltrating lymphocytes may also result in indirect decreases in the release of proinflammatory cytokines, signalling proteins (peripheral inflammatory proteins) known to mediate tissue damage.

In the heart, S1P1 is expressed on atrial myocytes and may be associated with regulation of heart rate. S1P1 agonism activates both G alpha i (Gi) and β-arrestin signalling pathways. β-arrestin activation leads to receptor internalisation, while Gi coupled signalling activates GIRK channels that regulate potassium efflux and membrane potentials. Synthetic S1P receptor modulators have demonstrated transient, first dose associated, chronotropic (slowing of HR) and dromotropic (slowing of AV nodal conduction) effects, based on cardiomyocyte S1P1 signalling, that are on target and dose dependent. S1P receptor modulators activate both Gi agonism and GIRK activation as well as β-arrestin internalisation of S1P1. Synthetic S1P receptor modulators result in sustained S1P1 internalisation leading to a decrease in receptor density at the cell surface. Thus, subsequent exposure to an S1P1 modulator has less impact on the GIRK channel with less effect on HR and AV conduction. Thus, at therapeutic levels, the largest reduction in HR and conduction typically occurs with the first dose and lessens upon repeat dosing.

Etrasimod is the fifth substance to be licensed in the EU within the class of S1P modulators. Four S1P receptor modulators have previously been licensed (comprising fingolimod [Gilenya], siponimod [Mayzent], ozanimod [Zeposia], and ponesimod [Ponvory]. All 4 were licensed initially for the indication multiple sclerosis (relapsing, relapsing remitting, secondary progressive different for the different substances). Only ozanimod has already been licensed for a second indication, which is ulcerative colitis. Etrasimod is therefore the first substance of this group of substances that is aiming at a non-CNS related indication in the first place.

The claimed indication reads as follows:

"TRADENAME is indicated for the treatment of patients 16 years of age and older with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or an advanced treatment."

The CHMP did not accept the term advanced therapy in the indication as this is clearly defined in the EU and refers to a medicine for human use that is based on genes, cells or tissue engineering. Development and approvals of advanced therapies are a subject to specific guidelines, requirements, directives and legally binding regulations (e.g. Regulation (EC) No 1394/2007) which did not apply for the development or approvals of medicinal products such are JAKi or biologics.

The applicant amended their claim to "advanced immunomodulators" (referring to biologics and small molecules). However also the number of patients included in Phase 3 studies which have been treated with small molecule immunomodulators with a specific mode of action (i.e. JAKis) was limited to 53 patients overall, and to 24 patients not having also received a biologic previously.

The efficacy in this subpopulation of 24 patients with JAKi only (a total 50 with exposure to JAKis and biologics) pre-treatment showed similar response to the overall population but only for the short-term treatment since there were almost no patients in the chosen response-efficacy categories with a previous JAKi treatment only in the long-term part of study 301 (only for the endpoint symptomatic remission, with an evaluation based on 10 patients). A conclusion on "similar efficacy" in those with JAKi pre-treatment was not considered acceptable by the CHMP based on these results.

Accordingly, the applicant amended the indication further and the approved indication reads as follows:

Velsipity is indicated for the treatment of patients 16 years of age and older with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy, or a biological agent.

The proposed dose is 2 mg daily irrespective of age and/or body weight. The compound is recommended to be administered with food for the first 3 days to attenuate potential transient heart rate lowering effects related to initiation of treatment and can then be administered without recommendation regarding food intake. The claimed age range for treatment, as seen above, is 16 years and above. However, the proposed PI includes a warning statement for the use in elderly patients above 65 years of age. It also includes a warning for patients (especially referring to patients aged 16 and 17) with a body weight below 40 kg due to increased plasma levels of etrasimod. No dose adjustments are proposed for patients with renal or hepatic (mild and moderate) impairment. The compound is contraindicated in patients with a short-term (6 months) history of cardiovascular disease (e.g. Myocardial infarction (MI), Heart failure (HF, and stroke), with a history of 2nd or 3rd degree AV block, sick sinus syndrome, and SA-block. The compound is also contraindicated in patients with immunodeficiency, severe active acute and chronic infections, and active malignancies. In addition, since the compound is teratogenic, there is a contraindication for pregnant women and women of childbearing potential not using effective contraception.

The applicant includes several precautions for treatment initiation, including the conduct of an ECG, evaluation of concomitant medication as well as monitoring of patients for at least 4 hours, which can be extended to 8 hours depending on the evaluation of vital signs (HR) and ECG.

The product is presented as an immediate release film-coated tablet.

2.3. Type of application and aspects on development

The applicant presents as proof of efficacy, a phase 2 dose-finding trial, as well as two phase 3 pivotal trials in a population that has had insufficient response to a wide variety of treatments. A couple of features of the programme deviate from what is considered the current "standard", referring to the proposed population, as well as the trial design. A description of these deviations is given below. Despite these deviations, the overall development was found to be acceptable.

According to the applicant the development program for etrasimod to treat moderately to severely active UC was formally discussed with the United States Food and Drug Administration (FDA), the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) and the appointed (Co-)Rapporteurs. Relevant consultations with the EU regulatory authorities regarding the clinical development program and marketing application submission plans for etrasimod in UC are briefly described in the table below.

Table 1: Etrasimod ulcerative colitis US and EU regulatory interactions

European Union		
EMA CHMP SAWP/European Network for Health Technology Assessment meeting	Discuss key elements of etrasimod UC Phase 3 program, including definition of moderately to severely diseased population of MMS 5 to 9 to include subjects with MMS 4, other study population elements, statistical analyses, proposed safety monitoring procedures; DDI studies; and acceptability of planned MAA safety database	Scientific Advice, dated 27 June 2019
EMA CHMP SAWP request for advice	To confirm acceptability of the proposed regulatory starting materials for the manufacture of drug substance.	Scientific Advice, dated 24 February 2022
Rapporteur (BfArM), Co-Rapporteur (HALMED) and EMA meeting	Pre-submission interaction to prepare for MAA submission, including discussion on indication statement, warnings and safety monitoring, and efficacy analyses, including the following: • Corticosteroid-free endoscopic improvement at Week 52 • Corticosteroid-free symptomatic remission at Week 52 Primary and key secondary endpoint analyses excluding subjects who only failed prior oral 5-ASA and/or had isolated proctitis	Pre-MAA Meeting summary, dated 25 August 2022

The main issues in the scientific advice of 2019 pertained to the following issues:

- Overall study design for the two pivotal studies: The advice accepted that long-term efficacy was investigated in one of the two studies only, despite the fact that this study used a different design as compared to other developments in the field ("treat-through-design" instead of "randomised withdrawal"). It was, however, recommended that the placebo use be restricted to 6 months and include an active comparator arm in such a study, in order to avoid too high rates of treatment/study discontinuation. It was, however, acknowledged that the design could still be adequate to assess benefit/risk.
- The target population with a severity of MMS 4-9 was considered acceptable based on the required severity for the colon mucosa, provided that an adequate discussion on severity would be provided at the time of MAA (for final decision on this point: see below).
- The potential inclusion of patients having been treated with mesalazine only was also considered problematic, and adaptation of the criteria, to exclude such patients was recommended. Also, more clear definitions of pretreatment courses were recommended to be defined, especially for biologics in order to ensure that patients would have received optimal/optimised treatment before inclusion. The overall heterogeneity of the patients was also mentioned as a potential drawback.
- The inclusion of patients with proctitis was on one hand welcomed (since these are otherwise usually excluded from trials in UC) but it was recommended not to include these patients in the primary analysis population.

- The inclusion of adolescents from the age of 16 was endorsed.
- A main part of the discussions was related to the proposed endpoints and the applicant was made aware of the fact that the proposed endpoints were not compliant with the requirements of the CHMP UC guideline, since no co-primary evaluation of symptomatic and endoscopic remission was planned to be included. The applicant was also made aware that both would need to be evaluated with a "steroid-free" criterion for the time-point week 52 in the long-term trial. The applicant was recommended to consider the set-up of different SAPs for the FDA and EU, in order to account for divergent requirements.
- The applicant was also made aware to implement an estimand strategy according to the ICH E9 addendum, and the requirements thereof for the context of UC clinical trials according to the CHMP UC guideline. Since a problem with missing values (due to treatment and/or study discontinuation) especially in the long-term trial was already identified, sensitivity analyses, including a tipping point analysis was recommended.
- The advice also discussed the pharmacology programme. This was overall considered acceptable, including the omission of the metabolites from the DDI studies based on the presented preliminary data from a mass balance study. A DDI study with oral contraceptives was recommended based on the known teratogenicity of the compound.
- The planned safety evaluations were mainly considered acceptable, however, some reinforcements were recommended.
- The overall size of the safety databased was considered low, and potentially not compliant with the E1 guideline.

The applicant implemented these recommendations only partly into their development.

With regard to the definition of the patient population, the FDA recommended a definition of moderately to severely active UC as an MMS of 5 to 9, but agreed that with the proposed incorporation of RB score of ≥ 1 the MMS of 4 to 9 was reasonable as an inclusion criterion and also recommended that the primary analysis for both studies be conducted on subjects with MMS 5 to 9, including ES of ≥ 2. This recommendation was implemented by the applicant.

The second advice received in 2022 dealt with issues related to the chemical, pharmaceutical and biological development. In this advice, the following issues were discussed:

- The starting materials: No agreement on the acceptability of the starting materials AR402140 and AR413584 for the manufacture of etrasimod drug substance was achieved. A redefinition to earlier steps/significant structural fragment(s) was recommended. The proposed starting material AR413584 was considered acceptable with recommendation to provide additional information within the MAA.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as film-coated tablets containing 2 mg of etrasimod. The product contains the etrasimod L-arginine salt.

Other ingredients are: Tablet core – Magnesium stearate (E470b), Mannitol (E421), Microcrystalline cellulose (E460i), Sodium starch glycolate (Type A). Tablet coating - Brilliant blue FCF aluminium lake (E133), Indigo carmine aluminium lake (E132), Tartrazine aluminium lake (E102), Macrogol 4000 (E1521), Poly(vinyl alcohol) (E1203), Talc (E553b), Titanium dioxide (E171).

The product is available in a HDPE bottle with a polypropylene cap and integrated desiccant, or aluminium blisters laminated to an oriented polyamine (oPA) film and integrated desiccant layer (HDPE/LDPE), with a paper/aluminium/LDPE backing as described in section 6.5 of the SmPC.

2.4.2. Active substance

2.4.2.1. General information

The chemical name of etrasimod free acid is (*R*)-2-(7-(4-cyclopentyl-3- (trifluoromethyl)benzyloxy)-1,2,3,4- tetrahydrocyclopenta[b]indol-3-yl) acetic acid corresponding to the molecular formula $C_{26}H_{26}F_3NO_3$ It has a relative molecular mass of 457.48 g/mol. The structure of the arginine salt is shown in the following figure:

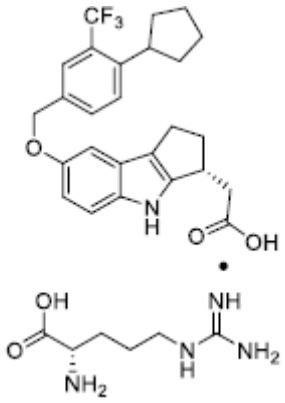


Figure 1: active substance structure

The chemical structure was elucidated by a combination of MS, ^{1}H and ^{13}C-NMR, FTIR and elemental analysis. The solid-state properties of the active substance were measured by XRPD.

The active substance is a powder, and it is non-hygroscopic. The active substance has poor aqueous solubility which worsens at acidic pH. Due to the poor solubility of the active substance, a routine control of particle size distribution is included in the specification in view of the potential impact on finished product performance.

Etrasimod exhibits stereoisomerism due to the presence of one chiral centre. The absolute stereochemistry of the active substance was confirmed using single-crystal x-ray diffraction. The chiral centre originates during the manufacture of the active substance and after introduction of the starting materials. Enantiomeric purity is controlled routinely by chiral HPLC.

Polymorphism has not been observed for etrasimod, only one solid state has been observed (form I), and this is thermodynamically stable.

2.4.2.2. Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided and is considered satisfactory. The active substance is manufactured at one site. Etrasimod is synthesised in five main steps using well defined starting materials with acceptable specifications.

Suitable definition and specifications for the materials have been defined.

Critical steps of the manufacturing process are identified. The respective critical process parameters are defined including normal operating ranges (NORs) and proven acceptable ranges (PARs) defined based on experimentation.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Changes introduced during scale up were minor, these have been presented in sufficient detail and have been justified. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The active substance is packaged in LDPE bags which comply with EC 10/2011 as amended.

2.4.2.3. Specification

The active substance specification includes tests for appearance, identity (IR), assay (HPLC), impurities (HPLC), enantiomeric purity (Chiral HPLC), L-Arginine content (titration), water content (KF), residual solvents (HSGC), residue on ignition (Ph. Eur.), and particle size (laser light diffraction).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set. The limit for unspecified impurities is set in line with ICH Q3A.

Limits for residual solvents have been set in line with ICH Q3C requirements. A risk assessment for elemental impurities was performed in line with ICH Q3D principles and the risk of elemental impurities is considered negligible.

The justification for the absence of routine control of microbiological quality and potential polymorphism is accepted.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data of 11 commercial scale batches of the active substance are provided. Supportive batch analysis data from earlier small-scale batches were also provided. The results were within the specifications and consistent from batch to batch.

2.4.2.4. Stability

Stability data from three commercial scale batches of active substance from the proposed manufacturer stored in a container closure system representative of that intended for the market for up to 36 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. In addition to this, supportive information was provided for one batch from a pilot scale batch from a separate manufacturer that was used during development. 60 months of long-term data was available from this supportive study. Photostability testing following the ICH guideline Q1B was performed on one batch, and the active substance is sensitive to light.

The following parameters were tested appearance, assay (HPLC), impurities (HPLC), enantiomeric purity (Chiral HPLC), water content (KF), particle size (laser light diffraction). Additional testing was also performed for polymorphic form (XRPD) and microbiological quality (Ph. Eur.). The analytical methods used were stability indicating.

Under long term and accelerated stability testing conditions, all tested parameters were generally within specifications, degradation products increased but conformed to specification requirements. One exception was noted for some stability samples from one specific batch. For this batch, out of specification results were obtained for degradation products. The applicant conducted an investigation, and the results demonstrate that for this particular batch, the out of specification results were caused by improper preparation of stability samples during testing. This was also supported by later analysis of the same batch showing no further out of specification results for degradation products.

Results on stress conditions under dry heat, moist heat, acidic, alkali and peroxide exposure were also provided on 1 batch. The dry and moist heat studies were conducted in the solid state, while the remaining studies were conducted in the solution phase. In the solid phase, very minor degradation was observed, whereas in the solution phase, a significant decrease in assay and corresponding increases in impurities were observed.

The stability results indicate that the active substance manufactured by the proposed supplier(s) is sufficiently stable. The stability results justify the proposed retest period of 36 months with the applicant's selected storage condition of "store in sealed double LDPE bags in a HDPE container and at 15 to 25°C."

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The finished product is a film-coated tablet containing etrasimod arginine equivalent to 2 mg etrasimod. The tablets are green, round and approximately 6 mm in diameter debossed with ETR on one side and the number 2 on the other.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The aim of pharmaceutical development was to develop an immediate release formulation suitable for the target population. The active substance is poorly soluble in aqueous media across the physiological pH range and is regarded as BCS class II. With respect to particle size, a regular control is included in the active substance specification. Only one polymorphic form of the active substance has been observed, and this form is thermodynamically stable. Polymorphism of the active substance does not therefore impact finished product performance.

During early development (phase 1 & 2 studies) a powder in capsule formulation was developed for use. Later in development a tablet formulation was developed for use in the clinical trials (phase 2 & 3 studies). The 2 mg tablet proposed for commercial use is slightly different as compared to the 2 mg tablet used in the phase 2 & 3 trials. The content of the diluent (mannitol), and lubricant (magnesium stearate) along with the film-coating agent are altered for the commercial formulation. These changes were made to improve manufacturability of the commercial dosage form. The applicant performed bioequivalence studies to compare the early capsule clinical formulations to the later tablet clinical formulation. With respect to the commercial 2 mg formulation, a bioequivalence study was also performed to compare this to the earlier formulation, please refer to the clinical section for further details on the bioequivalence studies performed. *In-vitro* dissolution comparisons were also performed.

Considering the low content of the active substance and a noted instability to mechanical stress, direct compression was selected as the method of manufacture. To prevent tablet picking the content of magnesium stearate was optimised during the development of the commercial formulation. The

manufacturing process was shown to be robust throughout commercial scale up. During development content uniformity following blending and lubrication steps was assessed and found to be acceptable

The QC method proposed for dissolution testing was initially not considered acceptable, the concentration of surfactant was not considered to be demonstrated to be as low as possible. In addition to this, the increased paddle rotation speed was not justified, the limit had not been set in line with the performance of the bioequivalent batch, and the investigation of discriminatory power was not sufficient. These aspects were raised as part of a major objection. To resolve the major objection the applicant developed an updated dissolution method, where the speed of the paddle apparatus was reduced, and a lower concentration of surfactant was implemented. The regular limit proposed for QC release using this updated method was then acceptably set in line with the performance of the bioequivalent batch. The applicant provided sufficient data on the investigations performed concerning the discriminatory properties of the proposed dissolution method. These included quantitative alterations in the amount of disintegrant and lubricant used in the formulation, the manufacture of tablets with increased hardness, and evaluation of particle size ranges of the active substance. Despite these extensive investigations, it was not possible to demonstrate discriminatory properties with respect to these specific aspects. The data provided was considered a comprehensive investigation package, and the revised dissolution method uses a surfactant level and paddle speed aimed at maximising the discriminatory potential when considering this formulation. The major objection was therefore considered resolved, and the revised method is considered acceptable.

The primary packaging is a HDPE bottle closed with a polypropylene cap, desiccant integrated directly into the cap or an aluminium blister strip laminated to an oriented polyamine (oPA) film and integrated desiccant layer (HDPE/LDPE), with a paper/aluminium/LDPE backing. The materials comply with Ph. Eur. and EC requirements where relevant. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.4.3.2. Manufacture of the product and process controls

The manufacturing process consists of five main steps: pre-blending, blending, compression, film-coating, and packaging. The pre-blending step involves the initial blending of a portion of the mannitol to coat the blending equipment. The remaining excipients and active substance are then added, and the main blending step commences. There are several sifting steps included during blending. Following generation of the final blend, a direct compression process is used to generate the uncoated tablet. This is then film-coated and packaged into the container closure system. The process is considered to be a standard manufacturing process and is conducted at one finished product manufacturing site.

The applicant has presented a process validation protocol related to the prospective validation to be performed on the commercial scale batches. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

2.4.3.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form appearance, identification (HPLC, chiral HPLC), content uniformity (Ph. Eur.), assay (HPLC), degradation products (HPLC), dissolution (HPLC), water content (Ph. Eur.), and microbiological quality (Ph. Eur.).

The limit for unspecified impurities has been set in line with relevant ICH Q3B guidance. The applicant proposed to include two degradation products in the specifications. For one of these impurities the relevant qualification threshold is exceeded, and toxicological qualification at the relevant levels has been performed.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. In addition, batch analysis data on 3 pilot scale batches were provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and analysis conducted, it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed (considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). The initially provided nitrosamines risk assessment was not acceptable and a major objection was raised. The applicant was requested to provide descriptions of methods and analysis performed to support the proposed no risk conclusion. Additionally, the applicant was requested to assess the potential for the carry-over of relevant amines into the finished product. The applicant addressed the major objection by providing details of the methods and analysis used to support the conclusions. The potential risk from the carry-over of vulnerable amines into the finished product was also addressed by the further scientific rationale and data provided in the response. Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The initially proposed limit for QC dissolution was not accepted, as this was not set in line with the performance of the bioequivalent batch. As this could impact *in vivo* performance, this aspect was also included in the overall major objection on the dissolution method proposed. The applicant resolved this portion of the major objection by setting the dissolution limit in line with the bioequivalent batch analysed with the revised dissolution method.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided on three batches manufactured at 70% of the proposed commercial batch size, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.4.3.4. Stability of the product

Stability data from three pilot scale batches of finished product stored for up to 24 months under long term conditions (30ºC / 75% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) were provided in each of the proposed container closure systems. The batches are representative of those proposed for marketing and were packed in the primary packaging proposed for marketing. The long term conditions applied are not fully in line with ICH recommendations as 75% RH is applied rather than the 65% RH recommended for long term testing by ICH. This deviation from guidance was accepted and the use of an increased humidity would pose a greater challenge to the product as compared to the ICH recommended condition. The long term stability of the finished product was acceptable even under these more challenging conditions.

Samples were tested for appearance, assay (HPLC), degradation products (HPLC), dissolution (HPLC), water content (Ph. Eur.), enantiomeric purity (HPLC), disintegration time (Ph. Eur.) and microbiological quality (Ph. Eur.). The analytical procedures used are stability indicating. The finished product is stable

under the long term and accelerated conditions studied. Increases in specified and total degradation products can be seen during the stability studies, however the increases are relatively minor, and the product remains within specification in both proposed packaging formats. Compared to the blister presentation, the bottle presentation shows a slightly higher but within specification increase in degradation.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The finished product is not considered sensitive to light.

With respect to ongoing stability studies, in accordance with EU GMP guidelines, any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

In-use stability testing was conducted to simulate to the anticipated use of the HDPE bottle presentation. The results of this testing showed that no in-use shelf life for the opened bottles was necessary. Under normal simulated use the product remained stable beyond the time typically needed to take all doses.

The packaging components contain a desiccant component. The SmPC includes instructions to store in the original package to protect the product from moisture which is considered appropriate.

Based on available stability data, the proposed shelf-life of 36 months without specific temperature storage instructions and the requirement to store in the original package to protect from moisture as stated in the SmPC (section 6.3) are acceptable.

2.4.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

During the procedure two major objections on Quality had been raised, the first concerning the information initially presented to support the nitrosamine risk evaluation, and the second concerned the initially proposed method for QC dissolution testing. To resolve the major objection on nitrosamine impurities the applicant provided further information to substantiate their no-risk conclusion. For the second major objection concerning the dissolution method the applicant developed a revised method. The proposed limit for QC dissolution testing was set in line with the bioequivalence batch and information was provided on the investigation of the discriminatory potential of the dissolution method. Following the provision of the information, these major objections were considered to be sufficiently resolved.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendations for future quality development

N/A

2.5. Non-clinical aspects

2.5.1. Introduction

All pivotal non-clinical studies have been performed compliant to GLP regulations and no deviations from European guidelines have been identified. In-vivo toxicology studies have been performed via the oral route, the clinically intended route. Durations of non-clinical repeated-dose toxicology studies (up to 6 months in rodents (rats) and up to 9 months in non-rodents (dogs)) support the clinically intended chronic use.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

The applicant performed a broad range of *in vitro* and *in vivo* studies to prove the concept of etrasimod's primary mechanism of action via activation of sphingosine 1-phosphate (S1P) receptor 1 (S1P1), a cell surface-expressed protein shown to regulate lymphocyte egress from lymphoid organs.

On the in-vitro level, the applicant mainly used β-arrestin recruitment assays and GTPγS binding assays as readouts for the two main signalling cascades resulting from receptor binding to S1P receptors. In a β-arrestin recruitment assay using human $S1P_{1-5}$ receptors recombinantly expressed in HEK293 cells, etrasimod was found to be a potent, full agonist at the $S1P_1$ receptor (half maximal effective concentration [EC_{50}] = 6.10 nM) with a relative efficacy of 110% (compared to the endogenous ligand S1P) and a partial agonist at $S1P_4$ and $S1P_5$ receptors (EC_{50} values of 147 nM and 24.4 nM, respectively) with relative efficacies of 63% and 73% of the S1P response, respectively. Neither agonistic nor antagonistic activity could be demonstrated at $S1P_2$ or $S1P_3$ receptors. In similar β-arrestin recruitment assays etrasimod was determined to be as well a potent full agonist on mouse, dog, and monkey $S1P_1$ receptors with similar mean EC_{50} values, ranging from 3.65 to 8.70 nM (mean efficacy > 80% S1P), across species. According to PK calculations, the expected concentration of the drug in humans at 2 mg therapeutic dose is 220 nM (65 – 370 nM).

Etrasimod was found to have similar potency compared to ozanimod and siponimod at inducing β-arrestin recruitment through the $S1P_1$ receptor, which is according to the applicant the receptor principally involved in lymphocyte count reduction and is the desired pharmacological activity of etrasimod. Compared to etrasimod, the M3 and M6 metabolites of etrasimod were 10 × and 3 × less potent than etrasimod at the $S1P_1$ receptor regards β-arrestin recruitment.

Regarding the potency of etrasimod at inducing GTPγS binding through the same receptor ($S1P_1$ receptor) the potency of etrasimod (EC_{50} = 57 nM) was closer to that one of the endogenous ligand (S1P, EC_{50} = 156 nM) compared to ozanimod (EC_{50} = 1 nM) and siponimod (EC_{50} = 4 nM).

In a receptor internalisation assay in CHO cells expressing human $S1P_1$ receptors etrasimod showed equivalent potency for receptor internalisation compared to other S1P receptor modulators (IC_{50} values between 1 and 9 nM) but a much higher potency compared to the endogenous ligand (S1P; (IC_{50} values 608 and 5212 nM; N=2).

Several *in vivo* immune mediated disease models showed a positive effect of etrasimod on the disease progression or even prevention: experimental colitis in mice, concavalin A-induced hepatitis in mice, prophylactic and therapeutic effect on MOG-induced experimental autoimmune encephalomyelitis in mice, FITC-induced contact hypersensitivity in mice, collagen-induced arthritis in rats.

In vivo studies confirmed that etrasimod induces the desired pharmacologic effect, a dose-dependent reduction of circulating lymphocytes in rodent models. Etrasimod can be considered as an immune-modulating drug.

Totality of primary pharmacology data indicate that etrasimod primary mode of action is potent $S1P_1$ full antagonism, resulting in internalizing the cell surface receptor and consequently reduction of immune cell egress from the lymph organs. This mechanism is adequately described and additionally measured as a biomarker in primary PD human studies.

2.5.2.2. Secondary pharmacodynamic studies

An in-vitro screening investigating the possible interaction of etrasimod with 97 receptor, ion channel, and neurotransmitter transporter targets other than S1P receptors, and with 13 enzymes did not yield evidence for relevant interaction of etrasimod with the investigated molecular structures.

2.5.2.3. Safety pharmacology programme

In a GLP-compliant in-vitro hERG-assay etrasimod did not show a potential for inhibition of the cardiac hERG potassium current. Neither a GLP-compliant cardiovascular safety study in telemeterised conscious dogs, nor a GLP-compliant CNS safety study in male rats, nor a GLP-compliant respiratory safety study in plethysmograph restrained male rats yielded hints regarding hazardous effects on the respective organ systems.

2.5.2.4. Pharmacodynamic drug interactions

The applicant did not conduct pharmacodynamic drug interaction studies. This was considered acceptable by the CHMP.

2.5.3. Pharmacokinetics

2.5.3.1. Pharmacokinetic studies

The pharmacokinetics of etrasimod was investigated in several in-vitro and in-vivo studies. This includes studies from early development up to studies performed in support of pivotal non-clinical and clinical investigations. Absorption was studied in-vitro and in-vivo after single and repeated dose administration in mice, rats, rabbits, dogs and monkeys. Studies in monkeys are limited to single dose, since monkeys were not further involved in the development. Distribution was studied in-vitro and in-vivo in pigmented and non-pigmented rats. The metabolism of etrasimod was investigated in microsomes, hepatocytes and in-vivo in mice, rats and dogs. Respective metabolic pathways were proposed. The enzymes involved in metabolism and potential metabolic inhibition, or induction was investigated in a set of experiments. Excretion of etrasimod and metabolites was studied in rats, dogs. In-vitro studies concerning pharmacokinetic interactions are partially presented in the non-clinical section of the dossier.

2.5.3.2. Methods of analysis

Distribution studies in rats and dogs were conducted with [^{14}C] etrasimod (APD334.DMPK.002 and Study APD334.DMPK.001) using liquid scintillation techniques (rats and dogs) and autoradiography (rats).

Plasma concentration of etrasimod in toxicokinetic studies in mice, rats, rabbits, and dogs was determined by the use of a validated LC-MS/MS methods. Validation is in compliance with the EMA *Guidance on Bioanalytical Method Validation.*

2.5.3.3. Absorption

Absorption was studied in in-vitro standard test systems and *in vivo*.

In-vitro

In-vitro studies are limited to two studies in Caco-cells investigating etrasimod´s bidirectional permeability across cell monolayers. The permeability across Caco-2 monolayers was high and based on the efflux ratios obtained, etrasimod is not a substrate of the efflux transporters P-gp and BCRP.

In-vivo

Single-dose

In-vivo studies with single dose administration have been performed in male in mice, rats, dogs and monkeys with intravenous and oral administration. Some studies have been performed as part of the toxicity studies (toxicokinetics) and the respective results obtained at day 1 were used as single dose data.

The plasmatic half-life after intravenous administration of 1 mg/kg etrasimod was 12, 8, 31 and 8 h in mice, rats, dogs and monkey respectively. The exposure 9.1, 7.0, 74.5 and 17.6 µg h/ml in mice, rats, dogs and monkeys respectively. Mean total plasma clearance was between 0.059 l/h/kg (monkeys) and 0.145 l/h/kg (rats), which was between 1 (dog) and 4% (monkey) of the hepatic blood flow of the respective animal species. The volume of distribution was 1.9, 1.6, 0.7 and 0.4 l/kg in mice, rats, dogs and monkeys respectively. These values were approximately 2 to 3 times greater than total body water for rodents, approximating total body water for dogs, and approximately 60% of total body water in monkeys.

After single dose oral administration of 1 mg/kg (mice and rats) or 3 mg/kg (dogs and monkeys), the maximum of plasmatic exposure was reached between 3.3 (monkeys) and 8.0 h (mice). Rats and dogs showed similar results as mice. Bioavailability was 100. 54, 73 and 44% of total dose in mice, rats, dogs and monkey.

The kinetic of etrasimod after single dose oral administration in fasted male and female mice (20, 60,200 mg/kg), male and female rats (25, 75, 150, 250 mg/kg), female rabbits (2, 10, 20 mg/g) and male and female dogs (2, 5, 10 and 15 mg/kg) was further investigated as part of the GLP-compliant toxicity studies. In this studies maximum of plasmatic concentration was reached within 2 (20 mg/kg etrasimod female mice) to 12 h (250 mg/kg etrasimod, male rat). The exposure was dose proportional in the dose range tested with a plasmatic half-live 5.96 and 31.0 h in rats and 24.8 and 33.7 h in dogs.

Repeated-dose

The kinetic of etrasimod after repeated-dose oral administration in fasted male and female mice (20, 60,200 mg/kg and 2, 6 and 20 mg/kg), male and female rats (25, 75, 150, 250 mg/kg and 2, 6, and

20 mg/kg), female rabbits (2, 10, 20 mg/g) and male and female dogs (2, 5, 10 and 15 mg/kg) was further investigated as part of the GLP-compliant toxicity studies.

After repeated administration, the maximum of plasmatic exposure was reached between 2.0 and 8 hours with no clear dose proportionality. The plasmatic half-life ranged between 5.09 (rats) and 80.1 h (dogs).

Plasmatic accumulation was determined by the use of an accumulation index ($AUC_{0\text{-last, last dosing day}}$/ $AUC_{0\text{-last, day1}}$). After daily oral administration to mice for 28 days, AI ranged from 0.858 to 1.31 in both sexes across the dose range evaluated. Following 3-month repeat-dose administration, AI values ranged from 0.67 to 1.40 in both sexes across the dose range evaluated.

The AI for male and female mice and male rats was between 1 and 2, suggesting steady-state exposure without significant accumulation of exposure over repeated dosing. AI values for pregnant female rabbits were slightly below 1, indicating a trend towards lower total exposure after 14 days of once daily dosing. However, the AI values for female rats and male and female dogs were generally above 2 (and above 3 for female dogs) indicating a propensity for accumulation at steady state in these species and sexes. The accumulation of etrasimod was slightly greater in dogs compared to rats. However, no obvious dose-related difference in AI within species or sex across any of the dose levels were noticed.

The TK data following repeated compared to single daily oral dosing in mice, rats, pregnant rabbits, and dogs indicate a trend towards earlier t_{max} across species at steady state and a potentially longer $t_{½}$ in dogs and rats at steady state. Sex differences at steady state in $AUC_{0\text{-last}}$ become more pronounced in rats. Although different doses were used in these 2 studies, the F:M ratio of $AUC_{0\text{-last}}$ after 182 and 364 days of dosing in rats was > 2 at all dose levels as compared to < 1.5 after the first dose. Taken together with the observations of higher AI values in female rats, there is a suggestion that repeated dosing in female rats may result in greater absorption and/or reduced clearance of etrasimod than observed in male rats, but these changes are subtle.

Exposures (C_{max} and $AUC_{0\text{-last}}$) of etrasimod increased in pregnant rats with increased dose levels, on GD6, GD17, and LD20. Etrasimod concentrations from rat pup plasma tended to increase with maternal dose with variable pup:maternal ratios ranging between 8.17 and 73.1% of the concentration observed in the maternal plasma (data not shown in this section). The data in juvenile rats are in line with the rodent PK data.

2.5.3.4. Distribution

In-vitro

In-vitro studies in different test systems showed, that etrasimod is highly protein bound (> 95%) in plasma of all nonclinical species and humans, and primarily distributes to the plasma compartment with low binding to the cellular component of blood.

In-vivo

Tissue distribution was investigated in non-pigmented and pigmented male and female rats and in pigmented following a single dose of [^{14}C]etrasimod, and repeat (7 days) dosing of [^{14}C]etrasimod at a target dose level of 10 mg/kg by oral gavage. [^{14}C]etrasimod distributed to tissues of GI tract, organs of clearance (kidney and liver), myocardium, secretory glands (adrenal and thyroid), and the non-circumventricular central nervous system tissues (spinal cord and brain) in non-pigmented and pigmented rats. Etrasimod also penetrated the blood:brain, blood:testes, and blood:follicle barriers in

both rat strains. Repeat dosing of Long-Evans rats (male and female) with [^{14}C]etrasimod resulted in increased exposure relative to rats of the same strain that received a single dose. The concentrations and exposure to radiocarbon were moderately higher for pigmented than non-pigmented skin (though less than 2-fold higher), in agreement with a moderate but not significant binding to, and retention of [^{14}C]etrasimod-derived radiocarbon in, melanin-containing tissues in Long-Evans rats (male and female). Blood-to-plasma ratios from [^{14}C]etrasimod studies were in a similar range to that reported in the *in vitro* assessment with no differences observed between Sprague Dawley and Long-Evans rats, or between sexes. The blood-to-plasma ratios of < 1 for all animals tested indicated that radioactivity stayed primarily in the plasma compartment with little distribution to the cellular component of blood

2.5.3.5. Metabolism

The metabolism of etrasimod was investigated *in vitro* in liver microsomes of mouse, rat, rabbit, dog, monkey and human, as well as hepatocytes of rat, dog, monkey and human. Furthermore, hepatocytes with recombinant human CYPs, Caco-2, MDCKII-BCRP, MDCKII-P-gp, and HEK293 cells were used. In-vivo studies were performed in rat and dog.

In-vitro

The metabolic turnover of etrasimod in liver microsomes of human, monkey, dog rat and mouse was low with a half live above 1 hour. In rabbits, the half live (approximately 30 minutes) was lower.

In liver microsomes of mouse, rat, rabbit, dog monkey and human 5 metabolites (M2, M3, M4 and M5) were qualitatively. The metabolites M1, M2 and M3 were found in the preparations of all species. M4 was identified in rabbit and M5 in mouse, rat, rabbit, monkey and human microsomes.

In hepatocytes of rat, dog monkey and human origin 29 metabolites could be identified. Monkey hepatocytes showed the highest turnover of [^{14}C]etrasimod followed by rat, human, and dog. In human hepatocytes 16 metabolites were found, with M3 and M6 as the most abundant metabolites (4.3 and 9.0% of total radioactivity). No such information is provided for the other species tested. Not all human metabolites were found in the microsomal preparations of at least one species involved in general toxicity studies (rat and dog). This concerns the metabolites M14, M15, M17 and M18.

In-vivo

The in-vivo metabolism was studies in mice, rats and dogs.

In mice, the in-vivo metabolism of etrasimod was investigated as part of a 90-day oral repeated dose toxicity (carcinogenicity) study at 20 and 200 mg/kg/day. 31 etrasimod-related components were identified. The predominant metabolites identified in animals administered 20 mg/kg/day were M28 [62 to 64% of the total peak area]) and an oxidised-etrasimod (M42 [17 to 21% of the total peak area]), while the predominant metabolites identified in animals administered 200 mg/kg/day were M6(19 to 22% of the total peak area), M28 (12 to 16% of the total peak area), and M29 (16 to 18% of the total peak area). The total peak areas appear generally increased between doses of 20 and 200 mg/kg/day after 90 days of dosing, but etrasimod- related material exposure was not dose-proportional.

In rats the metabolism of etrasimod was investigated as part of a mass balance study conducted in male and female Sprague Dawley bile duct intact rats and bile duct-cannulated rats (single oral dose at 10 mg/kg) and bile duct intact Long-Evans rats (7 daily oral doses of 10 mg/kg/day) with [^{14}C]etrasimod. In this study, etrasimod underwent extensive biotransformation to produce 29 radioactive components of which 25 were identified/characterised by LC-MS.

Unchanged [^{14}C]etrasimod was the predominant circulating radioactive component and represented 50.0 and 65.9% of the radioactive exposure through 48 hours for males and females, respectively. The most abundant circulating metabolite following a single dose was M6, which constituted an oxidation and dehydrogenation on the cyclopentyl ring of [^{14}C]etrasimod. M6 was present at 26.1 and 17.8% of the radiocarbon $AUC_{0.25-48}$ in males and females, respectively. Metabolite M3, which constituted an oxidation on the cyclopentyl ring of [^{14}C]etrasimod represented 7.27 and 9.40% of the radiocarbon $AUC_{0.25-48}$ in males and females, respectively. Minor metabolites, such as sulfate and glucuronide (< 2.5% of parent), were also observed in plasma. Metabolites M6 and M3 were among those present in feces, combined of 19.6 and 13.7% in males and females, respectively.

A separate study in BDC Sprague-Dawley rats profiled metabolites in bile following 10 mg/kg [^{14}C]etrasimod oral dose. The most abundant single, radioactive components in bile were M21 (oxy-didehydro-APD334 acyl glucuronide isomer-2) in males and M1 (APD334 acyl glucuronide-1) in females. Metabolites M20/M21/M22 (combined due to potential acyl migration *in vivo* and/or during sample processing) represent 22.7% of the dose recovered in male rat bile and 11.9% of the dose recovered in female rat bile. Likewise, M1/M30/M31 (similarly combined) represent 20.2% of the dose recovered in male rat bile and 22.9% of the dose recovered in female rat bile. Additional biotransformations were comprised of more extensive oxidation of etrasimod and represented less than 5% of the dose were M39, M42, M44, and M28, and the secondary glucuronide and sulfate conjugates of these oxidations, including M40, M45, M46, M47, M35, M48, and M49. Only 1 metabolite was quantified in male bile, but not female bile: M42 (trioxy-didehydro-APD334-2).

Metabolites were also profiled following a daily oral dose of 10 mg/kg [^{14}C]etrasimod for 7 days to bile duct-intact male and female Long-Evans rats. In general, the metabolic profile in Long-Evans rats was similar to Sprague Dawley rats with differences only in the extent of metabolite formation. M6 was the predominant circulating analyte in plasma pools from males administered multiple doses, and represented 48.0% of the radiocarbon exposure, compared with [^{14}C]etrasimod at 24.6%. The relative abundance of M6 in both sexes was higher after multiple doses than after a single dose in Long-Evans rats. The third most abundant peak characterised in the multi-dose plasma pools was M3, which constituted 7.77 and 6.68% of the radiocarbon $AUC_{0.25-48}$ in males and females, respectively, and was similar to that observed at single dose levels. The remaining metabolites quantitated in the plasma pools were under 2.5% of the $AUC_{0.25-48}$.

Metabolism was investigated as part of a mass balance study conducted in male and female beagle dogs following a single oral dose of 2 mg/kg [^{14}C]etrasimod. Etrasimod was moderately metabolised. A significant portion of the parent drug was eliminated via direct conjugation. The acylglucuronide was rapidly eliminated via the bile with subsequent hydrolysis in the GI tract releasing the aglycone for reabsorption back into systemic circulation. Additionally, the primary circulating analyte and recovered analyte in excreta was unchanged parent compound. The amount of radioactivity recovered in urine was less than 1.5% of the radioactive dose. The biotransformation of etrasimod in male and female dogs following a single oral dose resulted in the formation of 18 radioactive components, of which 11 of the analytes were identified/characterised by LC-MS.

In male and female dogs, the circulating metabolites and those recovered in feces were characterised as oxidative products of the cyclopentyl ring designated as M2, M3, M24, and M6. Additional metabolites of moderate abundance include secondary oxidation products (M26 and M43) as well as sulfate (M36) and acyl glucuronide migration products (M30 and M31) of the primary acyl glucuronide. In summary, the metabolism of etrasimod involved oxidation, dehydrogenation, and conjugation via sulfate or glucuronidation, with no notable metabolic differences between male and female dogs.

Enzymes involved in the metabolism of etrasimod.

The enzymes involved in the metabolism of etrasimod were further investigated in a set of 6 in-vitro studies. These studies were focused on the conversion of the metabolites M2, M3 and M6 and were performed in liver microsomes and recombinant human CYPs expressed in a baculovirus system. Etrasimod was poorly metabolised by human liver microsomes and the results were primarily obtained with recombinant human CYPs. The metabolizing enzymes identified in this set of studies were CYP2C8, CYP2C9, CYP3A4 and to a lesser extend CYP2C19 and CYP2J2. The main human metabolites M2, M3 and M6 were predominantly formed by CYP2C8 and CYP2C9 and to a lesser extent by CYP3A4, CYP2C19, CYP2D6 and CYP2J2. Investigations in human liver microsomes showed a unilateral transformation of M2 to M6 and then to M3, which was stable. It was further concluded, that M2 can undergo enantiomeric selective oxidation to M6 followed by reduction to M3 by cytosolic enzymes while M3 does not undergo interconversion to M6 or M2 with either cytosolic or microsomal enzymes.

Glucuronidation was investigated in liver microsomes from male CD-1 mice, Sprague Dawley rats, beagle dogs, cynomolgus monkeys, and pooled liver microsomes from humans of both sexes. The order of catalysis of etrasimod-glucuronide conjugation by rUGT enzymes was UGT1A7 >> UGT1A1 > UGT1A4 > UGT1A9 > UGT1A6 ~ UGT1A3 = UGT1A8. No glucuronide formation was observed for UGT1A10, UGT2B4, UGT2B10, UGT2B15, and UGT2B17. However, in clinical studies no relevant plasmatic levels of glucoronides could be identified. This leads to the conclusion, that that glucuronides are only formed to a small extended or rapidly cleared.

The ability of etrasimod to inhibit or induce the activity of metabolic enzymes was investigated *in vitro* in HLM (inhibition), rUGTs (inhibition), and rat and human hepatocytes (induction only).

The applicant has submitted 3 enzyme inhibition studies concerning the CYP system. The non completely guideline compliant study MRP-11-004 on human liver microsomal CYP1A2-, CYP2C8-, CYP2C9-, CYP2C19-, CYP2D6-, and CYP3A4-mediated metabolism which show that etrasimod may have the ability to inhibit CYP2C8-mediated reactions. Metabolism dependent effects (pre-incubation) and CYP2B6 were not investigated. The investigations concerning CYP2C9, CYP2D6 and CYP3A4 do not completely correspond with the guideline on drug interactions.

The study XT165088 confirmed, that CYP2C8 may be inhibited by etrasimod. However, since only 2 etrasimod concentrations (1 and 10 µM) were used in this study no Ki as requested by the guideline on drug interactions (CPMP/EWP/560/95) could be determined. There were no indications for metabolism dependent inhibition.

The third study APD334.DMPK011 investigated the influence of etrasimod on CYP2C8. The IC_{50} value of 4.0 µM. There was no evidence of time- or metabolism-dependent inhibition of CYP2C8 by etrasimod under these assay conditions.

Since the C_{max} for etrasimod (2 mg once daily) was described to be 0.247 µM [113 ng/mL]) (2.7.7 Summary of Clinical Pharmacology Studies), clinically relevant interactions with the CYP and UGT families appears to be unlikely from the non-clinical perspective.

The inducing ability of etrasimod was investigated in primary cultures of cryopreserved human and rat hepatocytes. In female rat hepatocytes, etrasimod was found to have little to no effect on CYP1A1, CYP1A2, and CYP3A1 mRNA levels at 3 and 30 µM concentrations in 3 cultures. However, etrasimod caused increases > 2-fold change on CYP2B1 (at 30 µM) and CYP2C11 (at 3 and 30 µM) expression in female rat hepatocytes. In male rat hepatocytes, etrasimod was found to have little to no effect on CYP1A1, CYP3A1, and CYP3A2 expression at 3 and 30 µM concentrations in 3 cultures. However, etrasimod caused increases > 2-fold change on CYP1A2 (at 30 µM), CYP2B1 (at 30 µM), and CYP2C11 (at 3 and 30 µM) mRNA levels in male rat hepatocytes.

Etrasimod (up to 10 µM) caused no induction of CYP1A2 mRNA levels in 3 preparations of cultured human hepatocytes. In 1 human hepatocyte culture, 10 µM etrasimod caused increases up to 3.73-fold

in CYP2B6 mRNA; however, the increases were less than 11% as effective as the positive control, phenobarbital, at inducing CYP2B6 mRNA levels. In 1 human hepatocyte culture, 10 µM etrasimod caused increases up to 8.94-fold in CYP3A4 mRNA; however, the increases were less than 10% as effective as the positive control, rifampin, at inducing CYP3A4 mRNA levels.

Considering the very low anticipated clinical etrasimod concentrations in the liver (6.8/ 156 nM), an inductive potential appears to be unlikely in the clinical setting.

2.5.3.6. Excretion

Excretion was studied by the use of [^{14} C]etrasimod in bile-duct cannulated and intact rats and in intact dogs.

Animals were administered a single dose of [^{14} C]etrasimod. Faeces and urine samples were obtained from male and female animals over a time period 168 hours and bile samples over 120 hours. Samples were analysed by liquid scintillation counting.

In intact rats etrasimod was mainly excreted via faeces. Approximately 87 to 89% of dose could be recovered within the first 48 hours. Total recovery was over 97% within 168 hours. Only round about 1% could be recovered from urine.

The investigations in bile duct cannulated animals (BDC) showed that, elimination was rapid, since more than 80% of the dose could be recovered within 24 hours. In BDC male and female Sprague Dawley rats, hepatobiliary excretion accounted for a mean of 80.6 and 64.8% recovery of radioactivity within 48 hours, and for a mean total of 83.0 and 66.7% of the administered dose, respectively for males and females. Urinary excretion was a minor (< 1%) contributor to the radiocarbon elimination in both cannulated males and females. The bile and urine data suggest [^{14}C]etrasimod was well absorbed (ranging from 67-84%) in males and females after oral administration. The overall mean recovery of radioactivity in BDC animals was approximately 100% of the radiocarbon administered through 168 hours postdose. No sex differences were observed in radiocarbon elimination.

In intact dogs, fecal excretion was the predominant route of elimination, accounting for a mean of > 81% of the administered dose of radioactivity through 168 hours postdose, with more than 68% recovered by 96 hours postdose. The mean daily recovery of radioactivity in feces beyond 96 hours postdose was approximately 2 to 7% each day for both sexes, suggesting the excretion of radioactivity was not yet complete by 168 hours postdose. Urinary excretion was a minor (< 2%) contributor to the elimination. The overall mean recovery of radioactivity for both sexes was > 83% of the radiocarbon administered. No sex differences were observed in radiocarbon elimination.

Taken together these studies indicate that the primary route of excretion is fecal in intact rats and dogs and that, based on the BDC rat, [^{14}C]etrasimod was well absorbed following oral dosing with hepatobiliary excretion being the major elimination route leading to fecal excretion.

In a human mass balance/excretion study (Study APD334-107) in healthy male subjects it was shown that radioactivity is excreted primarily in the feces with minor levels observed in the urine. Thus, data from animals and humans are consistent with hepatobiliary as the major elimination pathway.

No specific studies were conducted to investigate whether etrasimod passes the placenta.

No information is provided concerning potential excretion of etrasimod or its metabolites into the milk of lactating animals. However, plasma levels of etrasimod were determined in the pre-/postnatal development study in lactating dams and pups. Since etrasimod was detected in pup plasma samples,

milk transfer of etrasimod can be assumed. This information is included in section 5.3 of the SmPC. Velsipity should not be used during breast-feeding.

2.5.3.7. Pharmacokinetic drug interactions

Drug interaction studies were not performed in animals. One *in vitro* study was conducted to evaluate etrasimod as a substrate or inhibitor of human transporters (P-gp, BCRP, BSEP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1, and MATE2-K). Bidirectional cellular membranes or transporter expressing vesicles were incubated with enzyme specific substrate (for determination of etrasimod inhibition of transporter activity) or with etrasimod. Initial inhibition experiments were conducted at 10 and 100 µM. If needed, IC_{50} determinations were conducted at 0.03, 0.1, 0.3, 1, 3, 10, and 30 µM. For the substrate experiments, the compound was incubated at 1 and 10 µM residual etrasimod concentration determined by an LC-MS/MS method.

The results of this study showed that etrasimod inhibited P-gp, BCRP, and OATP1B1 with IC50 values of approximately 100, 35.7, and 10 µM, respectively, and caused less than 50% inhibition of the other transporters examined at concentrations up to 10 µM.

Since the concentrations used in this study (and the IC_{50} determined) are exceedingly higher than the concentrations to be anticipated during clinical use relevant drug interactions are not expected.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

Investigation of single dose toxicity in mice and dogs with oral doses of up to 1000 mg/kg bw was incorporated in two non-GLP dose-range finding studies in these two species. Not performing stand-alone single dose toxicity studies is accepted. One of three female mice at 1000 mg/kg bw was euthanised in extremis at day 4. In dogs no deaths occurred. MTD in dogs is considered to be > 1000 mg/kg. Overall, the acute toxicity of oral administration of etrasimod is considered low.

2.5.4.2. Repeat dose toxicity

Rat

In rats one non-pivotal non-GLP 14-day repeated dose toxicity study and three pivotal GLP-compliant repeated dose toxicity studies of 1, 3 and 6 months duration with a recovery period of one additional month were performed.

Effects seen in all three studies are consistent with each other and all three studies were performed using the oral route, the clinically intended administration route. The lowest dosage level in all three studies was 25 mg/kg bw/day. Toxic effect seems to worsen with time as it is seen with the mortality of animals and NOAELs set by the applicant. In the 14 days study, mortality is seen in the high dose group 1000 mg/kg and NOAEL is set at 300 mg/kg, while in the 28 days study mortality is seen already at 350 mg/kg on days 4-5 and NOAEL is set at 200 mg/kg. In the 3 months study there is no mortality in the high group – 200 mg/kg which is also the NOAEL, but in the subsequent 6 months study significant mortality is seen already at 250 mg/kg (19 animals on very different dosing days ranging from D 8 to D 178). Additionally, 4 animal deaths occurred at 75 (D 160) and 150 mg/kg/day (D 159, 79, 42) and were not considered etrasimod-related; 3 deaths were related to dosing injury, and 1 death was undetermined. NOAEL for the 6 months study is set at 150 mg/kg.

Already at the lowest dose (25 mg/kg bw) decreases in blood lymphocyte counts of about 75% were found and higher dose did not result in stronger lymphocyte count decreases, indicating already at the lowest dose a possibly saturating pharmacological effect of etrasimod.

Likely related to the pharmacological effect of etrasimod were decreased spleen weight and lymphoid changes characterised by an increase or decrease in the number of lymphocytes within specific lymphoid compartments of various lymphoid tissues.

Clear decreases in body weight gains were seen, starting already at the lowest dose and being most prominent at early time points. Decreases in food consumption were found as well. Increases in serum cholesterol and decreases in serum glucose and triglycerides may be correlated to decreased food consumption or body weight.

Possibly due to adaptive processes increases in liver weights were documented and histopathologically hepatocyte hypertrophy in both genders and at the highest doses necrosis of individual hepatocytes and increases in ALT in males were seen. Follicular hypertrophy in the thyroid may be based on the metabolic changes in the liver.

Mostly in female animals already at low doses, non-dose related increases in the weight of the lung plus the bronchi was observed. No histopathological correlate was found in the lungs.

In male animals decreases in prostate weights were noted, which showed, except in high dose (150 mg/kg bw) animals in the 6 month study, reversibility.

During the 1 month recovery phases most etrasimod affected parameters showed at least partial reversibility.

Already at the lowest dose level of 25 mg/kg bw used in the 6 month study, the AUC_{0-24} was determined being 97 times (210 µg*h/mL; in males) or 204 times (442 µg*h/mL; in females) the clinically intended exposure at 2 mg/day in humans (2.163 µg *h/mL).

Dog

In dogs two non-pivotal non-GLP 14-day repeated dose toxicity study and 4 pivotal GLP-compliant repeated dose toxicity studies were conducted, two studies of 1 month, and one study of 3, and 9 months duration each. All studies had a recovery period of one additional month.

All studies in dogs were conducted in males and females with oral administration, which is the intended clinical route. The studies were accompanied by toxicokinetics in the same animals. In general, no significant differences between males and females were noticed.

Since acute oral toxicity in dogs was rather low, very high doses of 100, 500 and 1000 mg/kg/ day were used initially (part A) in the first GLP-compliant 4 weeks study. Due to obvious toxicity, the dosing was initially suspended (drug holiday) and in the following reduced to 100, 200 and 300 mg/kg/day. However, these measures failed to improve the condition of the animals. The study was therefore restarted with animals receiving 20, 40 or 80 mg/kg/day by oral gavage (Part B).-

In the higher dose groups signs of general toxicity were apparent (vomitus/emesis, salivation, discoloured feces, red material in pan/bedding, incidences of thin appearance, loss of skin elasticity, and increased incidences of mucoid, soft, and watery feces, as well as lacrimation, decreased activity and on a single occasion for 1 animal, tremors). A dose dependent reduced weight and food consumption was observed during the time course of the study. These effects were at least partly reversible.

Effects on haematology parameters were limited to a decreased lymphocyte count in comparison to control, which is the anticipated pharmacological effect of etrasimod. This effect was, however, not

completely reversible during the recovery period. The lowering effects on leukocytes are considered of low magnitude and were mostly reversible.

Changes in erythroid parameters were noted at various magnitudes at doses above 40 mg/kg/day. At the end of the recovery period, the red cell parameters remained lower than respective controls but tended to be within expected ranges. A small prolongation of the APTT was observed.

The only adverse clinical chemistry findings were decreases in total protein, albumin, and globulins in all dose groups probably due to protein-losing enteropathy. Observations of dose-dependent decreases in calcium were noted and likely associated with, and secondary to, the decreases in albumin levels. Effects on chloride and total bilirubin were noted at various magnitudes at ≥ 40 mg/kg/day. Chloride increased in a generally dose-dependent manner from 80 mg/kg/day onwards. Total bilirubin also increased in a dose-dependent manner at doses ≤ 80 mg/kg/day. Increased total bilirubin is generally attributed to decreased red blood cell life span (haemolysis) or hepatobiliary injury. There were no other clinical pathology findings to differentiate these mechanisms. Infrequently, there may be direct biochemical inhibition of the uptake and excretion of bilirubin. Triglycerides were also decreased in the males at doses ≤ 80 mg/kg/day at termination.

Mean lung weights were significantly increased relative to controls in males and females from 20 mg/kg/day onwards correlated to oedema and/or alveolar histiocytosis. Mean thymus weights were mildly increased in some animals when compared to controls, which correlated to the oedema present microscopically. There were no etrasimod-related organ weight changes present in recovery male or female dogs.

Etrasimod-related macroscopic observations showed enlarged and/or red tracheobronchial lymph nodes and oedema in the thymus of males and females starting at 20 mg/kg/day. Microscopically, findings in tracheobronchial lymph nodes correlated to sinus erythrocytosis/erythrophagocytosis (described below). No macroscopic observations were present in recovery male or female dogs.

Etrasimod-related, non-adverse pathology findings were present in lungs, thymus, and tracheobronchial and mesenteric lymph nodes of both sexes starting at the lowest dose of 20 mg/kg/day.

Erythrocytosis/erythrophagocytosis was present in mesenteric lymph nodes of all terminal treated and control groups; however, there was a dose-dependent increased incidence of erythrocytosis/erythrophagocytosis in both sexes. At recovery, this finding was present in only 1 male at 40 mg/kg/day. Erythrocytosis/erythrophagocytosis was also present in tracheobronchial lymph nodes of all etrasimod-treated animals in the terminal and recovery groups. These lymph nodes were not saved and could not be examined microscopically from controls because all control dogs had been necropsied prior to the decision to include them as a potential target organ. Erythrocytes in lymph fluid is considered etrasimod-related, but the source of the erythrocytes could not be determined.

Overall, once daily oral gavage administration of etrasimod at dose levels of 20, 40, or 80 mg/kg to male and female dogs for up to 28 days elicited expected pharmacologic effects in clinical pathology as well as non-adverse histopathology findings. Adverse clinical observations, mean body weight losses, and decreased food consumption were elicited at doses ≥ 40 mg/kg/day. However, adverse clinical chemistry findings were noted at ≥ 20 mg/kg/day. Evidence of reversibility of all study findings was noted at recovery. A NOAEL was not established due to the adverse clinical chemistry findings.

Since no NOAEL could be established, a second 4 week study with much lower dosing groups of 0.02, 0.2 and 2 mg/kg/day was conducted. However, the profiles of the findings are comparable. Signs of general toxicity (soft/mucoid feces, salivation/thin appearance) are less pronounced. However, a

weight loss most likely due to decreased food consumption was apparent. Several changes in serum chemistry parameters (increase in chloride and decrease cholesterol and calcium concentration) were reversible and most likely connected to the low food intake during treatment. Other changes in haematology (decrease of leukocytes, eosinophils, basophils and other cells) and serum chemistry (decrease in calcium) are most likely connected to the main pharmacodynamics activity of etrasimod on lymphocytes. The decrease in lymphocytes is similar in all dose levels and not completely reversible. In accordance with the other pivotal studies absolute and relative lung weights were increased. This finding was again, correlated with alveolar histocytosis and in the higher dose group with fibrosis. Effects on lymph nodes, as expected were noted too.

Similar results like in the shorter-term studies were obtained in the 3 month study. The animals received 1, 5 and 15 mg/kg/day. Etrasimod induced mostly reversible bodyweight changes associated with decreased food consumption and other findings such as salivation, soft or mucoid faeces, which may be considered as signs of a general mild and not significant toxicity by the assessor. Changes of the serum chemistry parameters, which may be related to the decreased food consumption were observed. Mild effects on haematological parameters which were likely related to etrasimods pharmacological activity (decreased lymphocytes) were also noticed. With the exception of the decrease in lymphocytes, these effects were mostly reversible. Reversible findings concerning the thymus (increased weight, oedema) and lung (increased weight, alveolar histiocytosis, fibrosis) were observed. Lymphoid depletion is considered related to the decrease of the lymphocytes and therefore not adverse.

However, in this study, a hypertrophy/hyperplasia of the tunica media of the heart was apparent in all dosing groups.

Long term treatment with 2, 5, 10 or 15 mg/k/day over 9 months resulted in similar findings as described above. Weight loss due to a decrease in food-consumption was seen as well as signs of general toxicity which were less pronounced. However, concerning effects on the eye, aside from lacrimation, conjunctivitis and ocular discharge were diagnosed ≥ 5 mg/kg/day in males and ≥ 10 mg/kg in females at the end of treatment period. These findings were resolved after the recovery period.

Reversible changes in serum chemistry parameters and in haematology were observed like in the shorter-term studies. A decrease in lymphocytes, which was not completely reversible, was also noticed.

In accordance with the other pivotal studies, increased lung weights correlating with alveolar histocytosis and reversible fibrosis, effects on lymph nodes and on the thymus were observed again.

In contrast to the shorter-term studies, an irreversible reduced weight and size of the prostate were seen in all treatment groups. Effects on prostate weights were also noticed in all repeat-dose studies in rats. Therefore, a specific study investigating etrasimod’s effects on spermatogenesis was performed.

2.5.4.3. Genotoxicity

Etrasimod did not exhibit a biologically relevant genotoxic potential in a standard battery of genotoxicity assays. Although a slight increase in micronucleated PCEs was observed in females at the top dose of 300 mg/kg/d this finding is not considered clinically relevant. The exposure margin at the NOEL for genotoxicity of 150 mg/kg/d was 538 compared to clinical exposure at therapeutic dose of 2 mg/d. Etrasimod is considered to be devoid of clinically relevant genotoxic potential.

2.5.4.4. Carcinogenicity

Etrasimod was tested in two rodent lifetime bioassays to evaluate to tumorigenic potential of etrasimod. Bioassays were performed in Crl: CD1 (ICR) mice and Sprague Dawley rats. Increased incidence of haemangiosarcoma or haemangiomas in males and females at ≥ 6 mg/kg/day were detected in mice. The haemangiosarcomas were associated with macroscopic findings of cysts in the liver and oedema in the subcutis in males at 20 mg/kg/day and in red discoloration of some of the masses in the subcutis of females at 20 mg/kg/day. Commonly affected tissues were the liver, subcutis, heart, bone marrow, and spleen. A few haemangiosarcomas/haemangiomas were also noted in the uterus, intestine, skeletal muscle, lung, thymus, adrenal gland, kidney, eye, mesenteric lymph node, mesentery/peritoneum, spinal cord, and epididymides. The haemangiosarcomas and haemangiomas in males and females at ≥ 6 mg/kg/day occurred earlier in the study compared to those present in water control and control article groups. The number of haemangiosarcomas/haemangiomas present per affected animals was also increased in males at ≥ 6 mg/kg/day and in females at 20 mg/kg/day. Etrasimod-related non-neoplastic microscopic findings consisted of angiomatous hyperplasia in various tissues in males at 20 mg/kg/day and in females at ≥ 6 mg/kg/day (mostly uterus), various changes in the lungs (alveolar histiocytosis, alveolar eosinophilic accumulation, osseous metaplasia, and fibrosis) in males and females at ≥ 2 mg/kg/day.

The tumorigenic effect in mice with specific increased incidence in haemangiosarcomas or haemangiomas is considered a class effect for S1P receptor modulators as it has been observed for already approved S1P receptor modulators like fingolimod, siponimod or ozanimod. The results in lifetime rodent bioassays with etrasimod correlate also with respect to the bioassay in rats where no increased incidence of neoplastic lesions was detected. The NOAEL for neoplastic effects in mice was 2 mg/kg/d with a systemic exposure of 19 to 21 fold the human systemic exposure at therapeutic levels.

Haemangiosarcoma development in mice is considered to be triggered by stimulation of endothelial cells through S1P1 receptor (Pognan et al., 2018). S1P1 agonism in mice is considered to produce a sustained PIGF-2 (placental growth factor 2 release and induces constant VEC (vascular endothelial cell) mitosis. This is in contrast to humans and rats who do not react with PIGF-2 release or only transiently release PIGF-2. Therefore, sustained VEC stimulation and subsequent induction of haemangiosarcoma is not expected in these species.

There were no adverse or oncogenic etrasimod-related antemortem or postmortem effects observed in the rat study. There was focal thalamic mineralisation in the brain of both sexes at ≥ 2 mg/kg/day. Non-neoplastic findings were also observed in the liver of females administered etrasimod at ≥ 2 mg/kg/day and males at ≥ 6 mg/kg/day (increased hepatic foci of cellular alteration, and/or increased bile duct hyperplasia). The incidence and magnitude of most of these changes were similar across etrasimod-treated groups. It can be concluded there is no evidence of oncogenic effect.

2.5.4.5. Reproductive and developmental toxicity

A full set of reproductive toxicity studies was performed in rats and rabbits as requested by ICH S5 (R3). All pivotal studies were carried out in accordance with the relevant guidelines and in compliance with GLP regulations. However, it can be debated whether some of these studies could have been avoided. The receptor affected by etrasimod (sphingosine-1-phophate receptor) is known to be involved in vascular formation during embryogenesis. Accordingly, S1P receptor modulators were shown to have teratogenic effects.

Etrasimod did not show any effects on spermatogenesis and reproductive organs in male rats up to a dose of 200 mg/kg/day p.o. (MoE= 467) in a 28-day repeat-dose study, which was specifically performed to further investigate possible effects of etrasimod on male fertility.

Excessive toxicity was observed in pregnant rats in dose range findings (DRF) studies on embryo-foetal development at dose ranges that were not toxic after repeat dosing in non-pregnant animals. As a result, high dose dams had to be euthanised early after start of treatment and total post-implantation losses with no viable foetuses were noticed in all other dams in the first DRF study. In a second DRF study using lower doses, no marked maternal toxicity was observed. However, post-implantation loss was also a main finding and surviving foetuses showed malformations. Therefore, doses for female rats in all reproductive toxicity studies were reduced by a multiple.

Toxicokinetic data were obtained concomitantly with the studies on embryo-foetal development in rats and rabbits and the pre-postnatal development study in the rat. Data were used to calculate exposure margins at the NOAELs.

In the study on fertility and early embryo-foetal development there were no adverse effects observed on male and female fertility. The NOAEL for male fertility was at 200 mg/kg/day p.o. and at 4mg/kg/day p.o. for female fertility, respectively. Plasma etrasimod exposure (based on AUC) at the NOAELs was approximately 467 (males) and 21 (females) times that in humans at the recommended human dose.

In the study on embryo-foetal development in rats, doses of 0, 1, 2 or 4 mg/kg/day were orally administered to pregnant rats. Post-implantation loss with a corresponding lower number of viable foetuses was observed at 4 mg/kg/day. Etrasimod related external malformations (anasacra, oedema) were observed at 4 mg/kg/day. Visceral malformations and variations were noticed at all dose levels. Visceral malformations mainly concerned aortic vessel anomalies and septal defects. Skeletal variations were seen at 2 and 4 mg/kg/day. Maternal exposure (based on AUC) at the lowest dose tested was approximately 5 times that in humans at the recommended human dose. Relevant information on animal tests is outlined in section 5.3 of the SmPC. Etrasimod is contraindicated during pregnancy.

When etrasimod was orally administered to pregnant rabbits at 0, 2, 10 or 20 mg/kg/day, embryo-fetal toxicity was observed at mid and high doses. Post-implantation loss with a corresponding lower number of viable foetuses was noticed. Etrasimod related skeletal malformations (fused sternebrae) and variations (extra ossification sites) were noted at 20 mg/kg/day, respectively at 10 and 20 mg/kg/day. Visceral malformations relating to the aortic arch were seen at 10 and 20 mg/kg/day. There were no effects on embryo-fetal development at 2 mg/kg/day. Maternal plasma exposure (based on AUC) at the NOAEL was approximately 0.8 times that in humans at the recommended human dose.

Altogether, vascular malformations observed in rats and rabbits obviously relate to the role of the sphinosine-1-phosphate receptor during embryogenesis. Similar findings are seen with other S1P modulators. Therefore, etrasimod is contraindicated during pregnancy and the use of effective contraception while taking etrasimod is advised.

In the study on pre-/postnatal development in rats, dose levels of 0, 0.4, 2 and 4 mg/kg/day were orally applied. Etrasimod-related effects on natural delivery included one early termination due to severe signs during delivery in a high dose dam, an increase in gestation length and an increase of females with stillborn pups in mid and high dose groups. The NOAEL for F0 parturition is thus 0.4 mg/kg/day. An increased post-implantation loss was also observed in high dose dams. A decrease in F1 pup weight was noticed at all dose levels in the preweaning period as well as lower F1 pup viability in mid and high dose groups. High dose groups showed a reduced F1 fertility and reproductive performance (increase in pre-implantation loss, decrease in implantations). Plasma exposures (based on AUC) at the lowest dose tested was equivalent 1.1 times to those at humans at the recommended human dose.

Etrasimod was detected in plasma of F1 pups, indicating exposure from the milk of the lactating dams. Etrasimod should not be used during breast-feeding. This information is outlined in the SmPC.

Juvenile animal studies in rats were conducted to support the safe use of etrasimod in paediatric patients aged 2 to < 12 years old. Current application does not include children younger than 16 years of age. Juvenile animals tox studies are of no pivotal value.

2.5.4.6. Toxicokinetic data

Toxicokinetic data were obtained concomitantly with the studies on general toxicity, embryo-foetal development in rats and rabbits and the pre-postnatal development study in the rat and carcinogenicity in mice. Data were used to calculate exposure margins at the NOAELs.

2.5.4.7. Local Tolerance

There are no dedicated local tolerance studies. Local (gastrointestinal) tolerance was investigated as part of the general toxicity studies. There were no noteworthy findings.

2.5.4.8. Other toxicity studies

38 real or potential impurities in etrasimod, synthesis intermediates, starting materials or drug substance related molecules, have been identified and tested either in silico in two appropriate test systems (DEREK Nexus and SARAH Nexus) or GLP compliant AMES tests (AR413584 and AR432054). Of the 8 impurities classified as potentially mutagenic two (AR413584 and AR432054) were tested in bacterial reverse mutation assays with a negative result for AR413584 which then was classified as ICH M7 class 5. Therefore 7 impurities remained classified as either class 2 or class 3 mutagenic impurities according to ICH M7. All 7 class 2 or 3 impurities (Bromocyclopentane, AR432054, ethyl 2-oxyacetate, 4 Benzyloxyaniline, AR507614, 5-Me-AR507614, and AR438611) are controlled according to ICH M7 requirements in etrasimod drug substance to not more than 1.5 µg/d patient exposure.

Impurities AR426481 and AR402351, will be present in the etrasimod drug substance at ≤ 0.5%, which exceeds the 0.15% qualification threshold. In response to a request the applicant clarified that impurity AR401967 will be present in the drug substance and drug product at ≤ 1.0%, which likewise exceeds the 0.15% qualification threshold.

According to the applicant, all three impurities were present (to different extents) in the drug material used in the repeated dose toxicology studies. Impurity AR426481 was present 0.1% in the etrasimod preparation administered in the rat repeated dose toxicity studies of 3 months and of 6 months duration and the dog repeated dose toxicity studies of 3 months and of 9 months duration.

In the 6-month rat study already at the lowest etrasimod dose of 25 mg/kg bw the etrasimod exposure (AUC) was approximately 100 times the human exposure. Therefore, for impurity AR426481 the specification limit of ≤ 0.5% is considered toxicologically qualified.

Impurity AR402351 was present 0.14% in the etrasimod preparation administered in the rat repeated dose toxicity studies of 28 days duration and 0.38% in the etrasimod preparation administered in a dog repeated dose toxicity studies of 28 days duration. In the 28-day rat study already at the lowest etrasimod dose of 25 mg/kg bw the etrasimod exposure (AUC) was approximately 75 times the human exposure. Therefore, for impurity AR4202351 the specification limit of ≤ 0.5% is considered toxicologically qualified.

Impurity AR401967 was present 0.1% in the etrasimod preparation administered in the rat repeated dose toxicity studies of 28 days duration and 0.13% in the etrasimod preparation administered in a dog repeated dose toxicity studies of 28 days duration. In the 28-day rat study already at the lowest etrasimod dose of 25 mg/kg bw the etrasimod exposure (AUC) was approximately 75 times the human

exposure. Likewise, as for impurities AR426481 and AR402351, the specification limit of ≤ 1.0% for impurity AR401967 is considered toxicologically qualified.

Phototoxicity

Etrasimod did not demonstrate phototoxic potential in the BALB/c 3T3 mouse fibroblast assay. No further studies are needed.

2.5.5. Ecotoxicity/environmental risk assessment

Table 2: Summary of main study results

Substance (Etrasimod/Velsipity):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD123	log Dow (pH 5) > 6.25 log Dow (pH 7) = 5.11 log Dow (pH 9) = 3.48	Potential PBT (Y)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	> 4.5	
	BCF	1230	Not B
Persistence	$DT50_{sediment}$ (12°C)	> 1000 d	vP
Toxicity	$NOEC_{FISH}$	016 mg/L	not T
PBT-statement:	Not PBT or vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default	0.01 (free acid) 0.014 (API salt)	µg/L	> 0.01 threshold (Y)
Other concerns (e.g. chemical class)			(N)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	Koc soil: 40840, 64480, 63380 L/kg Koc sludge: 8156, 20035 L/kg Kd soil: 1552, 567, 279 L/kg Kd sludge: 2347, 6826 L/kg	
Ready Biodegradability Test	OECD 301 B	2,5%/ 28 d not readily biodegradable	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ water}$ = 8 d / 4.9 d $DT_{50,\ sediment}$ = >1000 d / 37 d $DT_{50,\ whole\ system}$ = 16.7 d / 18.9 d % shifting to sediment = 38.5/39.5 % CO2 = 5.2 / 9 % NER = 56 / 39.4 Transformation products > 10%: YES TP AR426481[1], max. 35.3% at d 3, DT_{50} = 10.1 – 19 d; **AR426481**: 2-[8-[[4-cyclopentyl-3-	system 1 / system 2 20°C at d 14 (Parent + NER) at test end at test end in whole system

		(trifluoromethyl)phenyl]methoxy]- 2,6-dioxo-1,3,4,5-tetrahydro-1-benzazocin-3-yl]acetic acid. TP AR435075[2], 31.6% at d 60, DT_{50} = 120 – 303 d **AR435075**: (1S,9S,12R)-6-[[4-cyclopentyl-3-(trifluoromethyl)phenyl] methoxy]-9-hydroxy-15-oxa-2-azatetracyclo [7.6.0.01,12.03,8]pentadeca-3(8),4,6-trien-14-one			in whole system, seems to be very persistent
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test *P. subcapitata*	OECD 201	NOEC	89	µg/L	growth rate
Daphnia sp. Reproduction Test, *D. magna*	OECD 211	NOEC	18	µg/L	length
Fish, Early Life Stage Toxicity Test; *P. promelas,*	OECD 210	NOEC	16	µg/L	Post-hatch survival
Activated Sludge, Respiration Inhibition Test	OECD 209	EC_{10}	1000	mg/L	respiration
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF	1230	L/kg	Calculated from BMF (dietary study)
Aerobic and anaerobic transformation in soil	OECD 307	DT50 parent DT50 TP AR435075 $\%CO_2$	< 1 44.2 – 155 12.6 – 33.8	d d %AR	20°C, 4 soils TP-AR435075 seems to be very persistent
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	EC_{10}	2.02	mg/kg	nitrification
Terrestrial Plants, Growth Test/*A. cepa*	OECD 208	EC_{25}	15	mg/kg	Shoot dry weight
Earthworm, Acute Toxicity Tests; *E. fetida*	OECD 207	NOEC	1000	mg/kg	Limit test, survival
Collembola, Reproduction Test; *F. candida*	ISO 11267	NOEC	1000	mg/kg	number of offspring
Sediment dwelling organism; *C. riparius*	OECD 218	NOEC	390	mg/kg	emergence

Etrasimod is not readily biodegradable and has to be considered very persistent in water/sediment systems and soils. Two major and one minor transformation products have been identified and IUPAC-names were determined. TP AR4350752 is considered vP. The bioaccumulation status needs to be assessed due to logDow values > 4.5 and lead to a BCF of 1230 indicating a bioaccumulation potential. However, Etrasimod does not meet the B-Trigger (BCF≥2000) and T-Trigger regarding the PBT assessment. Etrasimod is not considered a PBT nor vPvB substance.

Results from Phase II Tier A and Tier B assessment do not indicate any risks from etrasimod to surface water, groundwater, sewage treatment plants, sediments and the soil compartment.

2.5.6. Discussion on non-clinical aspects

Pharmacology

Etrasimod is considered being another member of the group of S1P receptor modulators. On the in-vitro level, the applicant mainly used β-arrestin recruitment assays and GTPγS binding assays as

readouts for the two main signalling cascades resulting from receptor binding to S1P receptors. The data obtained in the S1P receptor internalisation [study APD334.TS.012] indicate that etrasimod (and other S1P receptor modulators) exhibit a much higher potency regarding $S1P_1$ receptor internalisation (IC_{50} values between 8 and 9 nM) compared to the endogenous ligand S1P (IC_{50} values 608 and 5212 nM in the two experiments). In the β-arrestin assay of study APD334.TS.020 EC_{50} values for etrasimod (and other S1P receptor modulators) were in the range of the EC_{50} values determined for the endogenous ligand S1P (11 to54 nM and 21 nM, respectively).

As primary pharmacology animal model the applicant chose a model employing adoptive transfer of $CD^{4+}CD45RB^{high}$ T cells from WT mice to severe combined immunodeficiency (SCID) mice, which showed among other effects that 3 mg/kg bw of etrasimod significantly reduced the expression of the T cell and monocyte markers in isolated colonic tissue. In response to a CHMP request the applicant submitted the study documentation and an assessment of a recently performed non-GLP study (Study APD334.TS.036) evaluating etrasimod in a murine multidrug resistance gene 1a knockout mouse model (MDR1a KO) in which intestinal inflammation develops fully around 12-16 weeks of life. In this model once daily oral treatment with etrasimod at 1 or 3 mg/kg starting around week 7 for 35 days had dose-dependent, statistically significant beneficial effects on clinical and histopathological disease parameters.

Data on secondary pharmacology do not indicate relevant effects of etrasimod on molecular targets other than S1P receptors. In a GLP compliant in-vitro study it was demonstrated that etrasimod does not inhibit hERG currents.

Pharmacokinetics

The applicant has conducted detailed studies investigating absorption, distribution, metabolism and excretion of etrasimod in the different species used in toxicity testing.

The metabolic patterns in humans and species involved in toxicity has to be considered complex. Initially, no dedicated comparison between the different species and humans has been provided by the applicant. The most abundant metabolites in humans are M3 and M6 and the applicant was asked to compare exposure at steady state (which reflects the clinical setting) with the exposure obtained in animals after repeated dose since etrasimod and the metabolites M3 and M6 are prone to accumulation. Taking this into account, a more in depth assessment of the metabolic profile in the different species would have been of interest. However, based on the ICH guideline M3(R2) the applicant has provided an overview on the exposure to M3 and M6 in the toxicity studies based on short term single dose mass balance studies in rats and humans only. The overview shows that rats were exposed sufficiently to the metabolites M3 and M6 during toxicity testing. The exposure in mice and dogs was not investigated. Concerning etrasimod the species used in toxicity testing are considered adequate from the pharmacokinetic point of view. The exposure to M3 and M6 remains unclear in dogs and mice. The PK of metabolites M3 and M6 are further discussed in the clinical part of this assessment report.

General toxicity

In general, NOAELs set for the 1 month (150 mg/kg), 3 months (200 mg/kg) and 6 months (150 mg/kg) rat studies could be challenged. In response to a request the applicant argues that all findings in the TX10010, TX14004 and TX14009 studies were generally of minimal to mild severity, were not associated with clinical observations, did not compromise the health of the animals, and were largely reversible upon cessation of dosing in studies with recovery phases. These parameters are in line with recommendations from Kerlin and coworkers [Kerlin R, et al. Toxicol Pathol 2016;44(2):147-62.] and Palazzi and coworkers [Palazzi X, et al. Toxicol Pathol 2016;44(6):810-24.]. Even though, adversity is still a matter of scientific debate, applicant’s reasoning in this case is accepted.

In the one month study, there was a significantly lower body weight gain seen already in the 25 mg/kg group, prolonged APTT, elevated cholesterol and bilirubin; higher lung weights at necropsy, lower prostate weight, liver cell enlargement with occasional liver cell necrosis, higher adrenal gland weight. Even though lymphoid depletion is expected effect, there were also findings of necrotic lymphocytes were present within all lymphoid compartments (generalised) of various lymphoid organs in some animals with unscheduled deaths.

In the 3 months study, there was a centrilobular hepatocellular hypertrophy in the liver (not present in recovery animals) at all doses, higher liver weights in females at 25 mg/kg and in males at 100 mg/kg. Also, several clinical parameters were significantly changed already noted at 25 mg/kg and 100 mg/kg: elevated platelets, sporadic lower numbers of eosinophil, basophil, and unclassified cell counts, lower levels of glucose, triglycerides and total protein, higher cholesterol, total bilirubin, ALP, lower red cell mass, higher APTT and PT, higher creatinine.

In the 6 months study in all dose groups higher lung weight were seen at necropsy which persisted after recovery period, adrenal gland hypertrophy which reversed, higher liver weight at 75 mg/kg in males (in females at 150) correlated with microscopic hepatocyte hypertrophy; thyroid follicular cells hypertrophy (partially reversed) and atypical hyperplasia in the thymus (partially reversed). Thyroid follicular cell hypertrophy was considered to be associated with the liver hypertrophy, since increases in functional hepatocellular mass can cause thyroid proliferation through alterations in thyroxine metabolism and release of thyroid stimulating hormone from the pituitary. At 150 mg/kg increased thyroid and parathyroid weights are noted and decreased prostate weights, both persisted after recovery. In addition, at 25 mg/kg, besides the expected pharmacological effects, there was increased level of bilirubin, creatinine, BUN, and Cl; triglyceride was lower in males. At 75 mg/kg there was lower red blood cell mass, PT prolongation up to 2.1 x (only considered adverse at 250); lower glucose in F (in M at 150); higher cholesterol. At 150 mg/kg higher platelet count, generally resolved; APTT prolongation up to 2.3 x were noted.

Target organs identified in rat studies were liver, lungs, prostate and thyroid. Haematological and biochemical parameters affected are consistently PT and APTT, platelets, triglycerides, glucose, creatinine, cholesterol.

In dogs there is a clear pharmacologic effect of the drug in all treated animals seen as decreased number of lymphocytes and lymphoid depletion. Even though significant possibly adverse effects were seen at doses set by the applicant as NOAELs in the 1, 3 and 9 months studies in response to a request the applicant argues that all findings in the dog studies were generally of minimal to mild severity, were not associated with clinical observations, did not compromise the health of the animals, and were largely reversible upon cessation of dosing in studies with recovery phases. These parameters are in line with recommendations from Kerlin et al. and Palazzi et al. (please, see above). Even though, adversity is still a matter of scientific debate, applicant's reasoning in this case is accepted.

For the 4 week study with recovery period, NOAEL is set at the highest dose of 2 mg/kg regardless of effects seen even at lower doses. Decreased activity and gastrointestinal effects are seen in all dose groups sporadically (emesis, vomitus, salivation). Most worrisome finding is elevated lung weight which corresponds to microscopic alveolar histiocytosis at 0.2 mg/kg, while at 2 mg/kg this effect progrades to lung fibrosis.

Lung effect is a consistent finding in longer dog studies and they are seen below the NOAELs set by the applicant:

In the 3 months study, microscopic findings are seen in all dose groups sporadically, elevated lung weights at 1 mg/kg correlated with alveolar histiocytosis of the lungs, and fibrosis noted at 5 and 15 mg/kg.

In the 9 month study focal pleural fibrosis and focal pulmonary inflammation and increased lung weights are noted in all etrasimod-treated groups without a clear dose response and reversible.

Lung fibrosis was characterised primarily by a minimal thickening of pleura (surface of the lungs) by increased amounts of collagen (fibrosis). The overlying pleural mesothelial cells were slightly enlarged and increased in prominence. Lung fibrosis was still present in one recovery male. Alveolar histiocytosis in the lungs consisted of small aggregates of macrophages with vacuolated or eosinophilic cytoplasm randomly present within alveolar spaces. Alveolar histiocytosis was not present in recovery animals. These lung changes were considered test article related but not adverse based on the small degree of change.

Other findings in longer dog studies were GI symptoms – salivation, mucoid, soft feces; findings in the heart - hypertrophy/hyperplasia of tunica media in arteries of left ventricle, elevated APTT, decreased total protein, Cl, GGT, AST, ALT, cholesterol, bilirubin, prostate decreased in size and weight (not recovered).

In addition, hypertrophy/hyperplasia of the tunica media was observed primarily in the left ventricle of the heart. Effects on the shape of the vessels are described. This effect was observed ≥ 2 mg/kg/day and was not reversible during recovery. The applicant did not discuss this effect in depth and the potential relevance for clinical use remains unclear. However, the applicant added a description of these findings in the sections 5.3 and 4.4 of the SmPC. Section 4.4 now includes a warning that etrasimod should be used with caution in patients with severe respiratory disease (e.g., pulmonary fibrosis, asthma, and chronic obstructive pulmonary disease), which is acceptable.

Target organs identified in dog studies were lungs, gastrointestinal system, prostate. Haematological and biochemical parameters affected are APTT, total protein, Cl, GGT, AST, ALT, cholesterol, bilirubin.

It should be noted that it is a consistent finding in the dog studies that prolongation of the treatment results in additional findings such as enhancement of general toxicity. Since etrasimod shows a rather high accumulation index, accumulation in dog as an underlying mechanism cannot be excluded. Such increase in toxicity was not observed in humans.

Carcinogenicity

There is evidence of oncogenic activity from the long-term mouse study (haemangiomas and haemangiosarcomas occurred earlier in the study compared to those present in water control and control article groups. The number of haemangiosarcomas/haemangiomas present per affected animals was also increased in males at ≥ 6 mg/kg/day and in females at 20 mg/kg/day). Adequate exposure was reached, and effect is seen in 44 x higher exposure than in the human expected exposure. Malignancy is recognised as Important potential risk in the RMP, and routine risk communication measures are proposed (in SmPC sections 4.3 – contraindication; section 4.4 and 5.3).

Other non-neoplastic effects are in line with other toxicity studies, except there is no effect on rat lungs while in mice, a more severe adverse effect on lungs is seen (osseous metaplasia).

Reproductive toxicity

The full program of reproduction toxicity studies was performed as requested by ICH S5 (R3). The receptor affected by etrasimod (sphinosine-1-phosphate receptor) is known to be involved in vascular formation during embryogenesis. Accordingly, S1P receptor modulators were shown to have teratogenic effects. With regard to teratogenicity, a class effect can therefore be assumed. Velsipity is contraindicated during pregnancy and in women of childbearing potential not using effective contraception.

Excessive toxicity was observed in pregnant rats in dose range findings studies on embryo-fetal development at dose ranges that were not toxic after repeat dosing in non-pregnant animals.

Doses used in all of the reproductive toxicity studies in female rats had to be reduced by a multiple compared to the NOAEL obtained in repeat-dose studies. The highest dose in all pivotal reproductive toxicity studies was 4 mg/kg/day, whereas the NOAEL for female rats in the repeat-dose studies was between 150 and 250 mg/kg/day. This seems to be specific for etrasimod, since such a drastic dose reduction was not necessary for other S1P modulators to perform proper reproductive toxicity studies. Overall, the findings are in line with the role for S1P1 during embryogenesis and for what has been seen for other S1P receptor modulators. The applicant thus reasons that etrasimod is acting on the embryo/fetus directly rather than interfering with pathways in pregnancy maintenance. This argumentation can be followed.

Etrasimod did not show any adverse effect on male or female fertility. As expected, teratogenicity was observed in the embryo-fetal development studies in rats and rabbits already below human therapeutic exposures. In the study on pre-/postnatal development no maternal toxicity was observed, but etrasimod related effects on F0 delivery and F1 pre-and post-weaning development as well as on F1 fertility and reproductive performance.

Ecotoxicity/environmental risk assessment

Results from Phase II Tier A and Tier B assessment do not indicate any risks from etrasimod to surface water, groundwater, sewage treatment plants, sediments and the soil compartment. Etrasimod is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

Marketing authorisation can be recommended a non-clinical point of view. Etrasimod is not considered PBT nor vPvB and is not expected to pose a risk to the environment.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 3: Tabular overview of Phase 1 clinical studies

Study Identifier	Study Report Location	Study Title	Study Design and Type of Control
APD334-115	5.3.1.2	A Single-Dose, Open-Label, Two-Part Study to Evaluate the Pharmacokinetics, Cardiodynamic Effects, and Effect of Food Following Oral Administration of Different Etrasimod Controlled-Release Tablet Formulations in Healthy Adult Subjects	Open-label, 2-part single dose
APD334-007	5.3.1.2	A Phase 1, Randomized, Open-Label, Crossover Study in Healthy Subjects to Compare Relative Bioavailability of Etrasimod Tablets and Capsules	Open-label, randomised, 3-period crossover, single dose
APD334-114	5.3.1.2	A Phase 1, Open-Label, Randomized, Single-Dose, 3-Treatment, 3-Period Crossover Study in Healthy Subjects to Evaluate the Bioequivalence of Etrasimod 2 mg Proposed Commercial and Clinical Formulations, and to Assess the Effect of Food on the Pharmacokinetics of the Proposed Commercial Formulation	Open-label, randomised, 3-period crossover
APD334-001	5.3.3.1	Randomized, Double-Blind, Placebo-Controlled, Single Dose Escalation Study to Assess the Safety, Tolerability and Pharmacokinetics of APD334 Administered to Healthy Adult Subjects	Randomised, double-blind, PBO-controlled, single-ascending dose
APD334-002	5.3.3.1	A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Sequential, Ascending Multiple Dose Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of APD334 in Healthy Adult Subjects	Randomised, double-blind PBO-controlled, sequential, ascending multiple dose
APD334-107	5.3.3.1	A Phase 1, Open-Label Study to Evaluate the Absorption, Metabolism, and Excretion of [^{14}C]Etrasimod (APD334) Following a Single Oral Dose in Healthy Male Subjects	Open-label, nonrandomised, single dose
ES101001	5.3.3.1	A Randomized, Double-Blind, Placebo-Controlled Dose-Escalation Study in Healthy Chinese Adult Subjects to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics Characteristics of Etrasimod Following Oral Single and Multiple doses Administration	Randomised, double-blind, PBO-controlled, dose escalation
APD334-108	5.3.3.3	An Open-Label, Single-Dose, Parallel-Group Study to Assess the Pharmacokinetics of Etrasimod in Subjects with Mild, Moderate, and Severe Hepatic Impairment Compared to Healthy Matched-Control Subjects	Open-label, nonrandomised, single dose, parallel-group
APD334-109	5.3.3.3	A Single Blind, Placebo-Controlled Repeat Dose Study to Evaluate the Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of Etrasimod in Healthy Japanese and Caucasian Male Subjects	Single-blind, randomised, PBO-controlled repeat dose
APD334-112	5.3.3.3	A Phase 1, Open-Label, Single-Dose Study to Investigate the Effects of Renal Impairment on the Pharmacokinetics of Etrasimod	Open-label, single dose
APD334-009	5.3.3.4	A Phase 1, Open-Label, Parallel-Group, Fixed-Sequence Study to Assess the Effect of Fluconazole, Gemfibrozil, or Rifampin on the Pharmacokinetics of Etrasimod in Healthy Subjects	Open-label, parallel-group, 2-period, fixed-sequence
APD334-111	5.3.3.4	A Phase 1, Open-Label, Repeat-Dose, Two-Way, Single-Sequence Study to Evaluate the Effect of Etrasimod (APD334) on the Pharmacokinetics and Pharmacodynamics of a Monophasic Oral Contraceptive in Healthy Premenopausal Female Subjects	Open-label, 2-way, single-sequence, repeat-dose
APD334-116	5.3.3.4	A Phase 1, Open-Label, Fixed-Sequence, 2-Period, Crossover Study to Assess the Effect of Itraconazole on the Pharmacokinetics of Etrasimod in Healthy Subjects	Open-label, fixed-sequence, 2-period, crossover
APD334-008	5.3.4.1	A Randomized, Double-Blind, Placebo- and Positive-Controlled, Parallel-Group Study to Investigate the QTc-Exposure Response, Pharmacokinetics, Safety and Tolerability After Multiple Therapeutic and Supratherapeutic Dosing of Etrasimod (APD334) in Healthy Adult Subjects	Randomised, double-blind, PBO-and positive-controlled, parallel, multiple dose thorough QT

Study Identifier	Study Report Location	Study Title	Study Design and Type of Control
APD334-110	5.3.4.1	A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Cardiodynamic Effects of Five Different Etrasimod Dosing Regimens in Healthy Subjects	Randomised, double-blind, PBO-controlled

A more elaborate description of the phase 2/dose-finding study, and of the two pivotal phase 3 studies is given in the following:

Table 4: Description of studies in support of efficacy of etrasimod

Sites (n)	Start/End Date Subjects P/E/C/D[a]	Design	Study Treatment, Formulation, Duration	Primary Objective	Number of Subjects Entered[b] /Completed Study	Median Age Per Arm in Yrs. (Range)[c]	Sex M/F (subjects)	Primary Endpoint(s)
Study APD334-301 (Phase 3)								
268	13 Jun 2019/ 16 Feb 2022 420/433/207/227	Randomised, double-blind, PBO-controlled	Etrasimod 2 mg or placebo tablet qd, 52 weeks	Assess the efficacy of etrasimod on clinical remission in subjects with moderately to severely active UC	Etrasimod 2 mg: 289/161 Placebo: 144/46	40.0 (18, 78) 35.5 (17, 78)	M 240/ F 193	Clinical remission of UC per MMS at Week 12, clinical remission per MMS at Week 52
Study APD334-302 (Phase 3)								
239	15 Sep 2020/ 07 Dec 2021 330/354/316/38	Randomised, double-blind, PBO-controlled	Etrasimod 2 mg or placebo tablet qd, 12 weeks	Assess the efficacy of etrasimod on clinical remission in subjects with moderately to severely active UC	Etrasimod 2 mg: 238/213 Placebo: 116/103	37.5 (16, 73) 38.0 (17, 72)	M 208/ F 146	Clinical remission of UC per MMS at Week 12
Study APD334-003 (Phase 2)								
87	15 Oct 2015/ 14 Feb 2018 303/156/141/15	Randomised, double-blind, PBO controlled, parallel group	Etrasimod 1 mg, 2 mg, or placebo capsule qd, 12 weeks	Determine the effect of treatment in improving MMS	Etrasimod 1 mg: 52/47 Etrasimod 2 mg: 50/44 Placebo: 54/50	44.0 (21, 64) 38.5 (21, 67) 46.0 (20, 73)	M 32/ F 22	Change from Baseline in MMS at Week 12
Study APD334-005 (Phase 2)[d]								
51	25 Jan 2016/ 01 Nov 2018 118/118/97/21	Open-label extension	Etrasimod 2 mg tablet qd, 34 weeks	Long-term safety and tolerability	Etrasimod 2 mg: 112/92 Placebo: 6/5	45.0 (20, 72) 53.0 (33, 67)	M 71/ F 47	Long-term safety and tolerability

In addition to the efficacy studies, the following additional clinical studies are, or have been conducted:

Table 5: Clinical Studies not relevant form the claimed indication, or ongoing at the time of submission

ES101002	**5.3.5.1**	**A Phase 3, Randomized, Placebo-Controlled, Double-Blind, Multicenter Study to Evaluate the Efficacy and Safety of Etrasimod for Induction and Maintenance Treatment in Subjects with Moderately to Severely Active Ulcerative Colitis**	**Randomised, double-blind, PBO-controlled induction period, maintenance period, and open-label period**
APD334-303	5.3.5.2	An Open-Label Extension Study of Etrasimod in Subjects with Moderately to Severely Active Ulcerative Colitis	Open-label
APD334-006	5.3.5.4	A Phase 2a, Proof of Concept, Open-Label Study Evaluating the Efficacy and Safety of Etrasimod (APD334) in Inflammatory Bowel Disease Patients with Active Skin Extra-intestinal Manifestations	Open-label, single-arm, proof-of-concept
APD334-010	5.3.5.4	An Open-label, Pilot, Proof of Concept Study to Evaluate the Safety, Tolerability, and Efficacy of Oral Etrasimod (APD334) in Patients with Primary Biliary Cholangitis	Open-label, single-arm, proof-of-concept
APD334-011	5.3.5.4	A Phase 2a, Open-label, Proof of Concept Study to Determine the Efficacy and Safety of Etrasimod (APD334) in Patients with Pyoderma Gangrenosum	Open-label, single-arm, proof-of-concept
APD334-201	5.3.5.4	A Multicenter, Randomized, Double-Blinded, Placebo-Controlled 16-Week Study (with a 52-Week Open-Label Extension) to Assess the Safety and Efficacy of Etrasimod in Subjects with Moderate-to-Severe Atopic Dermatitis	Randomised, double-blind, PBO-controlled with open-label extension

Of the first two studies, no full study reports are submitted, but the following:

For Study ES101002: An "Interim Synoptic Clinical Study Report" is submitted. The is a combined induction and maintenance phase 3 trial (with re-randomisation of responders) conducted in the Peoples' Republic of China. The study is ongoing at the time of submission, and the report only includes blinded study-level safety data from the open-label period. Readers are therefore referred to Chapter 4.

Study APD-303: Also, for this study, an interim report ("interim snapshot report") is submitted. This is the long-term extension open-label study to the two phase 3 trials (but also to studies APD334-408, APD334-210, and APD334-203; see below) - which is currently still ongoing and proposed to provide long-term data up to 5 years. Some efficacy data have been submitted, generally being supportive to the results of the controlled studies. However, the primary objective of the trial is safety.

As can be seen from the table, the further four trials APD334-006, -010, -011, and -201 do not report data on the intended disease, but on different indications and have partly been terminated early due to poor recruitment.

The following studies were also ongoing at the time of submission, but have not been included in the above table by the applicant, and no documentation is submitted at this point of time:

- Study APD334-203 is a multicentre, randomised, double-blind, placebo-controlled, dose-ranging Phase 2 study to evaluate the efficacy and safety of etrasimod 1 and 2 mg once daily in Japanese subjects with moderately to severely active UC. The study consists of a 12-week induction treatment period, and a 4-week follow-up period. The primary endpoint is the proportion of subjects achieving clinical remission at Week 12.
- Study APD334-210 is a multicentre, randomised, double-blind, placebo-controlled, Phase 2 study to evaluate etrasimod 2 mg once daily in subjects with moderately active UC; as such patients with lower severity, (MMS = 4 to 6; ES ≥ 2, RB ≥ 1) at baseline were recruited compared to the main clinical program. The study utilises a treat through design consisting of a

12-week induction treatment period, 40-week maintenance treatment period, and 4-week follow-up period. The primary endpoint is the proportion of subjects achieving clinical remission at Week 52.

- Study APD334-308 is a Phase 3, multicentre, double-blind, placebo-controlled extension of Study APD334-302 to evaluate the efficacy and safety of etrasimod 2 mg once daily in Japanese subjects with moderately to severely active UC. The study consists of a 40-week treatment period and a 4-week follow-up period. The primary endpoint is the proportion of subjects achieving clinical remission at Week 52.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

The PK of etrasimod (APD334) has been evaluated mostly by noncompartmental analysis in an extensive set of 15 Phase 1 studies (Table 5), reaching from SAD, MAD, relative BA/BE, BE, human mass balance and thorough QT/QTc studies, to studies in special populations and drug interaction studies.
In addition, etrasimod plasma PK parameters (e.g., Ctrough, Cavg trough,ss) based on sparse sampling were obtained from patients with UC in two phase 2 and two phase 3 studies (Table 4) by summarising plasma concentrations at and across discrete timepoints.

The Phase 1 studies involved PK assessments from a total of 641 healthy volunteer subjects, including 22 subjects with hepatic impairment and 8 subjects with renal impairment. The Phase 2 and 3 studies involved PK assessments from 629 UC subjects treated with etrasimod (314 UC subjects received placebo). Furthermore, population PK modelling was applied.

Etrasimod is a weak acid and appears to classify as low soluble drug according to BCS [CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **]. The efficacious daily dose is 2 mg of etrasimod (free acid) dosed as an IR formulation. Etrasimod appears to be highly permeable, with little to no transport by the efflux transporters P-gp and BCRP based on not fully guideline conform *in vitro* studies.

While several studies explored various dose titration schemes, the AR will focus on the 2mg strength of etrasimod q.d. since it was what was used in the pivotal studies.

Absorption

A formal absolute bioavailability study in humans has not been conducted.

Etrasimod appeared in the systemic circulation following oral administration of etrasimod L-arginine with median tmax ranging from 3.5 to 8 hours post dose in healthy adult subjects following single oral doses from 0.1 mg to 5 mg etrasimod across studies under fasting conditions and following multiple doses from 0.7 to 4 mg once daily.

In fed state, median tmax ranged from 4 to 6 hours following single oral doses of 2 mg etrasimod, and etrasimod may be administered regardless of food as far as PK exposure parameters are concerned (see below).

While oral bioavailability of etrasimod has not been conclusively determined, observations from [^{14}C]etrasimod human mass balance study (APD334-107) suggest it may likely be rather high. Following administration of a single oral dose of etrasimod formulated as oral solution of 2mg/mL [^{14}C]etrasimod at a nominal specific activity of 100 µCi / 2 mg, absorption of administered radioactivity into the systemic circulation was judged quite extensive, based on the relatively low content of unchanged parent drug in the excreta (see chapter Elimination below). Based on comparison of Cmax

for plasma etrasimod and plasma total radioactivity of 41.5 ng/mL and 49.9 ng·eq/g, etrasimod appeared to be absorbed mostly unchanged (~83%), suggesting low first pass metabolism (*Table 8*).

Consistent with metabolites of etrasimod contributing significantly to circulating total radioactivity exposure in plasma, maximal levels of total radioactivity in plasma and whole blood were reached later in a human mass balance study, with median tmax values of 6.01 and 7.01 hours postdose, respectively.

While etrasimod plasma concentrations appeared to decline in an apparent monophasic manner after reaching Cmax, with an arithmetic mean (SD) t1/2 of 37.8 (3.22) hours, levels of total radioactivity in plasma and whole blood appeared to decline in a biphasic manner with an arithmetic mean (SD) t1/2 of 89.0 (8.52) and 78.0 (10.8) hours, respectively.

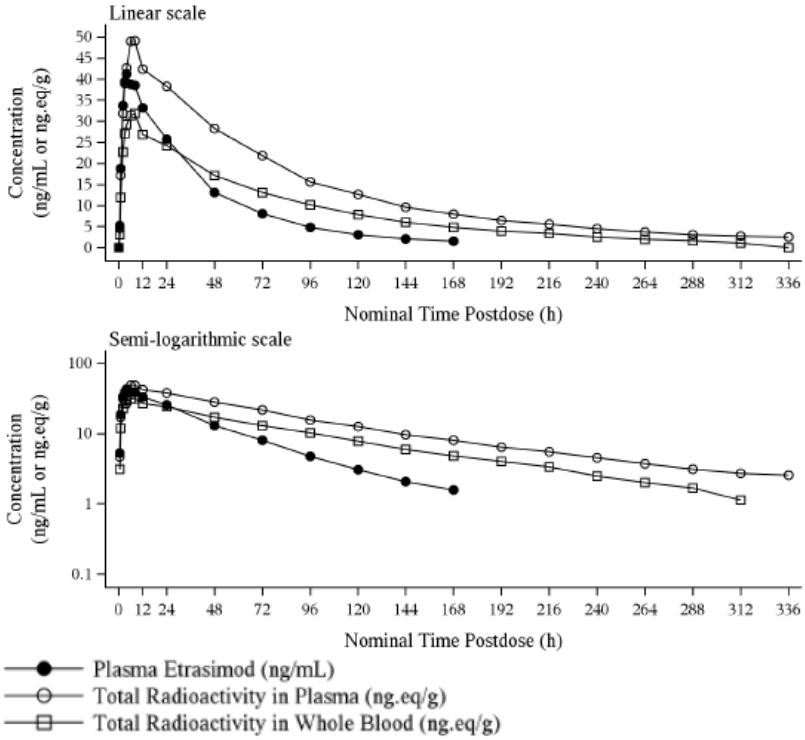


Figure 2: Arithmetic Mean Concentration-Time Profiles of Corrected Etrasimod in Plasma (ng/mL) and Total Radioactivity in Plasma (ng equivalents/g) and Whole Blood (ng equivalents/g) following a Single Oral Dose of 2mg [14C]-Etrasimod (~ 100µCi of [14C]) (Linear and Semi-logarithmic Scale)

Note: Plasma etrasimod concentrations were corrected by multiplying by correction factor 1.55 to account for the composition of the study drug (radiolabelled + non-radiolabelled).

Table 6: Summary of PK Parameters of Etrasimod in Plasma and Total Radioactivity in Plasma and Whole Blood following a Single Oral Dose of 2mg [14C]-Etrasimod (~ 100µCi of [14C])[Geometric mean (geometric CV%) unless otherwise indicated]

Parameter	**Plasma Etrasimod (N = 8)**	**Plasma Total Radioactivity (N = 8)**	**Whole Blood Total Radioactivity (N = 8)**
	[Geometric mean (geometric CV%)] unless otherwise indicated		
Cmax (ng/mL or ng.eq/g)	41.5 (22.7)	49.9 (18.9)	33.0 (14.8)
tmax (h)*	4.00 (3.00, 8.00)	6.01 (6.00, 8.00)	7.01 (6.00, 8.00)
tlast (h)*	168.00 (168.00, 168.00)	336.00 (312.00, 336.00)	312.00 (216.00, 336.00)
AUC0-t (h*ng/mL or h*ng.eq/g)	1740 (31.4)	4250 (22.5)	2610 (24.2)
AUC0-168 (h*ng/mL or h*ng.eq/g)	1740 (31.4)	3550 (21.4)	2220 (20.3)
AUC0-312 (h*ng/mL or h*ng.eq/g)	N/A	4210 (22.4)	2620 (22.1)
AUC0-∞ (h*ng/mL or h*ng.eq/g)	1820 (32.6)	4580 (22.4)	2810 (23.5)
t1/2 (h)+	37.8 (3.22)	89.0 (8.52)	78.0 (10.8)
CL/F (L/h)	1.10 (33.3)	N/A	N/A
Vz/F (L)	59.6 (26.0)	N/A	N/A
Cmax Plasma Etrasimod/ Total Radioactivity Ratio	N/A	0.832 (18.4)	N/A
AUC0-t Plasma Etrasimod/ Total Radioactivity Ratio	N/A	0.409 (11.1)	N/A
AUC0-∞ Plasma Etrasimod/ Total Radioactivity Ratio	N/A	0.397 (12.5)	N/A
Cmax Total [^{14}C] Radioactivity Blood/Plasma Ratio	N/A	N/A	0.662 (6.8)
AUC0-t Total [^{14}C] Radioactivity Blood/Plasma Ratio	N/A	N/A	0.614 (3.8)
AUC0-∞ Total [^{14}C] Radioactivity Blood/Plasma Ratio	N/A	N/A	0.612 (3.6)

*Median (minimum, maximum) is presented for tmax and tlast. +Arithmetic mean (SD) results are presented for $t_{1/2}$. Note: The corrected plasma etrasimod concentrations, multiplied by a ratio of 1.55 to account for composition of [^{14}C]etrasimod, were used to conduct the PK analysis. Source: APD335-107 CSR.

Four formulations of etrasimod were relevant in clinical studies supporting this MAA (*Table 9*). These were immediate release (IR) capsule formulations (powder-in-capsule; PIC), IR film-coated tablet formulations (clinical and commercial) and extemporaneously prepared oral solutions (EPS).

Comparable etrasimod PK exposure parameters were observed following single oral doses of 2mg etrasimod formulated as EPS and the solid oral dosage IR formulations (PIC, clinical and commercial tablets) across the human mass balance and biopharmaceutical Phase 1 studies (*Table 7*). A relative bioavailability study was submitted to provide bridging between the 2 mg capsule formulation (used in SAD, MAD and the Phase 2 studies) and the 2mg clinical tablet formulation used in most Phase 1 and the pivotal studies (APD334-007, *Table 7*) in the fasted state. Subjects (n=14) were enrolled and treated in the study in three groups of 10, 2 and 2 subjects, respectively. To substantiate that the three groups were not exposed to different conditions affecting the overall results, a sensitivity analysis involving the first and largest group of n=10 subjects only would be needed. However, since the overall evidence available from other studies with the clinical tablet formulation is consistent with the early results of the capsule formulation, study APD334-007 is not considered decisive and the issue is not pursued.

Bioequivalence between the 2mg clinical tablet formulation and the 2mg commercial tablet formulation proposed to be marketed has been demonstrated under fasting conditions in bioequivalence study APD334-114.
For the proposed commercial 2mg IR tablet formulation, mean (% CV) plasma Cmax, AUC0-t, and AUC ∞ values for etrasimod were 41.1 (26.8%) ng/mL, 1590 (32.4%) ng·h/mL, and 1660 (33.7%) ng·h/mL, respectively, following single dose administration in healthy subjects.

Table 7: Summary of PK parameters from Clinical Biopharmaceutic Studies [arithmetic mean ±SD)

Study Number	**Study Objective**	**Study Design**	**Subjects**		**Treatments (Product ID)**		**PK Parameters (arithmetic mean ± SD)**				
			No. [M/F]	**Mean Age (range)**	**Dose, Dosage**	**Form, Route**	**Cmax (ng/mL)**	**Tmax[a] (h)**	**AUC$_{0\text{-last}}$ (ng·h/mL)**	**AUC$_{0\text{-}\infty}$ (ng·h/mL)**	**t½ (h)**
APD334-107	To evaluate the absorption, metabolism, and excretion of [^{14}C]Etrasimod (APD334) following a single oral dose in healthy male subjects	Phase 1, open-label, non-randomised, single-dose study in healthy male subjects	8 M	31 ± 6.6 (21-44)	2 mg (Plasma Etrasimod)	Solution	42.5 ± 10.2	4.00 (3.00, 8.00)	1810 ± 552	1900 ± 596	37.8 ± 3.22
					2 mg (Plasma total radioactivity)		50.6 ±9.37 (ng-eq/g)	6.01 (6.00, 8.00)	4340 ± 921 (ng-eq·h/g)	4680 ± 980 (ng-eq·h/g)	89.0 ± 8.52

APD334-007§	To assess the relative bioavailability of 2 mg etrasimod tablets and 2 mg etrasimod capsules in the fasted sate and the relative bioavailability of 2 mg etrasimod tablets in the fed and fasted states	Phase 1, randomised, single-dose, open-label, 3-period, crossover study in healthy subjects	14 [7/7]	36.5 ± 4.59 (28-43)	2 mg, single dose	Capsule, oral (fasted)	45.5 ± 11.0	4.00 (4.00, 12.1)	1600 ± 335	1750 ± 399	36.7 ± 12.9
						Tablet, oral (fasted)	44.7 ± 11.0	4.00 (2.00, 4.00)	1600 ± 387	1710 ± 438	29.3 ± 4.28
						Tablet, oral (fed)	*45.0 ± 7.5*	*4.00 (4.00, 8.00)*	*1730 ± 384*	*1870 ± 444*	*31.5 ± 4.90*
APD334-114	To evaluate the bioequivalence of etrasimod 2 mg proposed commercial formulation and clinical formulation in the fasted state and evaluate the effect of food on PK of etrasimod 2 mg proposed commercial formulation	Phase 1, open-label, randomised, single-dose, 3-treatment, 3-period crossover study in healthy subjects	18 [10/8]	34.4 ± 9.37 (20-53)	2 mg, single dose	Clinical formulation (fasted)	45.1 ± 16.6	4.00 (4.00, 8.00)	1690 ± 553	1750 ± 585	35.9 ± 5.64
						Commercial formulation (fasted)	41.1 ± 11.0	4.00 (2.00, 12.00)	1590 ±517	1660 ± 560	35.3 ± 7.20
						Commercial formulation (fed)	43.8 ± 15.2	6.00 (1.00, 12.00)	1680 ±524	1750 ± 560	36.6 ± 7.00
APD334-115*	To assess the relative bioavailability of the test etrasimod CR prototype tablet formulation to the reference IR tablet in the fasted and fed state	Phase 1, single-dose, open-label, two-part study in healthy subjects	23 [11/12]	36.6 ± 9.0 22-55	2 mg single dose	IR-clinical formulation (fasted)	45.0 ±9.94	4 (2.50, 10.00)	1470 ±347	1510 ± 397	31.7 ± 5.14

[a] Tmax presented as median (minimum, maximum) F, female; M, male;

* PK parameters of IR-clinical formulation, but not CR formulation are included

[Source: APD334-007 CSR Table 4; APD334-107 Table 9; APD334-114 CSR Table 7; APD334-115 CSR Table 14.2.2.0]

§ In study APD334-007, comparison to fed cannot be accepted. Treatment C (etrasimod in fed state) was always administered in period 3 in this 2 treatment, 3 period study with 2 sequences only (ABC, BAC).

The influence of food on the bioavailability of etrasimod was studied for both the clinical and the commercial 2mg etrasimod tablet formulation in studies APD334-007 and -114, respectively (*Table 9*). The lack of a food effect was demonstrated for the commercial formulation in study APD334-114.
An attenuation of the effects on heart rate was observed when etrasimod was administered with food, hence it is recommended in the SmPC that etrasimod be administered with food for the first 3 days to attenuate potential transient heart rate lowering effects related to initiation of treatment. Etrasimod can then be taken with or without food.

Distribution

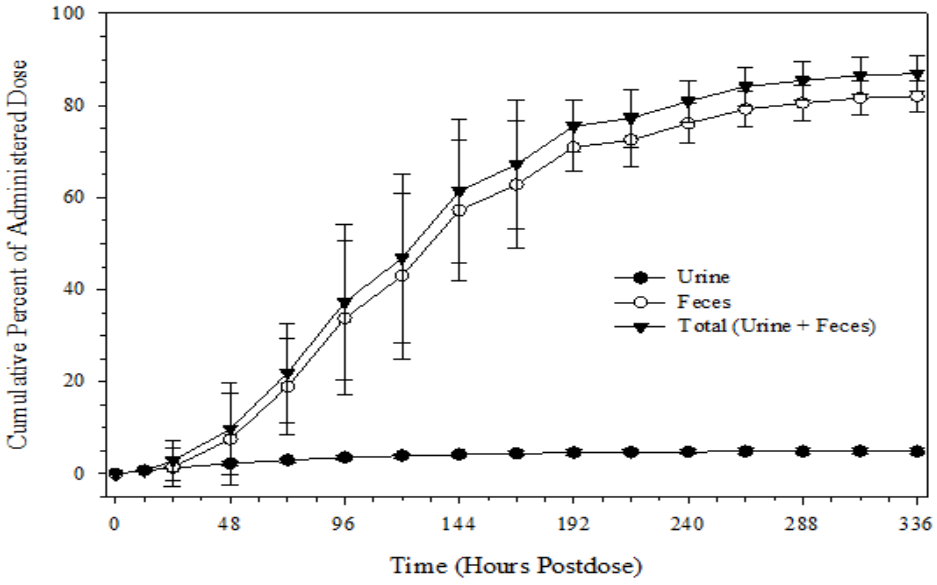
The mean (% CV) apparent volume of distribution during the terminal phase after oral administration (Vz/F) values ranged moderately from 50 (17.5%) to 86.7 (25.4) L in healthy subjects over the evaluated dose levels of 0.1 to 5 mg and across Phase 1 studies, suggesting distribution into tissues. Following repeat once daily dosing, mean (% CV) steady-state Vz/F values ranged moderately from 51.1 (19.0%) to 103 (31.6%) L over an etrasimod dose range of 0.7-3 mg once daily and across studies in healthy subjects and amounted to 66.2 (36.15) L on Day 21 for 2mg etrasimod q.d. in study APD334-002. Population PK modelling estimated that etrasimod apparent volume of distribution (Vss/F) at steady-state is 70 L.

Etrasimod was found to be highly plasma protein bound *in vitro* [mean (CV%) 97.9% (0.41%) at 10 µM] and similarly *in vivo* [fraction unbound 3.23% (58%) to 5.33% (30%)]. *In vitro*, albumin (HSA, < 0.1% unbound) and α1-acid glycoprotein (AGP, 1.1-1.4% unbound) appear to be the major contributors to the high binding of etrasimod in human plasma, followed by lipoproteins (14-17% unbound) at concentrations of 20 and 200 mg/mL (0.0437 and 0.437 µM).
With [^{14}C]etrasimod, the total plasma and blood drug related radioactivity concentration ratio was 0.6, indicating partitioning primarily to the extracellular component of blood.

Elimination

Based on [14C]etrasimod human mass balance study APD334-107, the major route of elimination in humans is hepatic, with minimal contribution by renal excretion based on 82% and 4.89% mean recovery of total administered radioactivity in faeces and urine, respectively.

The arithmetic mean (± SD) cumulative percent of radioactive dose recovered in urine, faeces, and total excreta is presented in Figure 3. A summary of the recovery of total administered radioactivity in urine, faeces, and total excreta is presented in *Table 8*.



Source: APD334—107, Radioanalysis Report Figure 2 Appendix 16.2.5.3

Figure 3: Arithmetic Mean (± SD) Cumulative Percent of Radioactive Dose Recovered in Urine and Faeces at Specified Intervals after a Single Oral Dose of 2mg [^{14}C]-Etrasimod (~ 100µCi of [^{14}C])

Table 8: Summary of the Recovery of Total Administered Radioactivity in Urine, Faeces, and Total Excreta within 336 Hours of 2mg [^{14}C]-Etrasimod (~100µCi of [^{14}C]) Administration

Analyte (Matrix)	Cumulative Ae (mg equivalents)	Cumulative Fe (%)
Total Radioactivity (Urine)	0.0980 (0.0150)	4.89 (0.647)
Total Radioactivity (Faeces)	1.64 (0.0764)	82.0 (3.47)
Total Radioactivity (Total Excreta)	1.74 (0.0878)	86.9 (3.78)

Note: The amount of total radioactivity excreted (Ae) and percentage recovery of radioactivity in the excreta (Fe) were calculated based on the actual radioactive dose of [^{14}C]etrasimod administered. Arithmetic mean (SD) data are presented. Source: APD334-107 CSR Appendix 16.2.5.3 Radioanalysis Report Table 6 and Table 8.

Unchanged etrasimod in faeces accounted for a mean of 11.2% of the administered radioactive dose.

No urinary excretion of unchanged etrasimod was detected, indicating that this is not a clearance pathway for the intact drug.

The mean (% CV) apparent oral plasma clearance CL/F after oral administration was low compared to hepatic blood flow across the Phase 1 studies and ranged from 1.13 (23.7%) to 1.43 (36.4%) L/h over the evaluated etrasimod single dose levels from 0.1 to 5mg in healthy subjects, and from 0.965 (19.9%) to 1.70 (16.6%) L/h over the evaluated multiple dose levels of 0.7 to 3 mg once daily, indicating low hepatic extraction.

The final model estimate of steady-state CL/F from population PK modelling was 1.06 L/h, based on evaluation of data pooled from healthy and UC subjects.

Etrasimod mean (SD) apparent terminal half-life (t½) values over single oral dose levels of 0.1 to 5 mg in healthy subjects across Phase 1 studies ranged from 28.1 (1.81) to 59.5 (14.8) hours, with an overall mean (SD) of 38.1 (7.63) hours (*Table 9*).

Following repeated dosing, etrasimod mean (SD) apparent terminal t½ values across multiple oral dose levels (0.7 to 3 mg once daily) in healthy subjects ranged from 33.3 (2.72) to 46.4 (7.81) hours across Phase 1 studies, with an overall mean (SD) of 40.0 (3.83) hours. The mean apparent terminal t½ tended to increase with longer PK sampling duration, suggesting a longer secondary terminal elimination phase.

Across both single and multiple-dose studies, the overall mean (SD) effective t½ was 30 (3.6) hours.

Table 9: Summary of Etrasimod Terminal and Effective Half-Life Values [Mean (SD)] Following Single- and Multiple-Dose Administration in Healthy Subjects

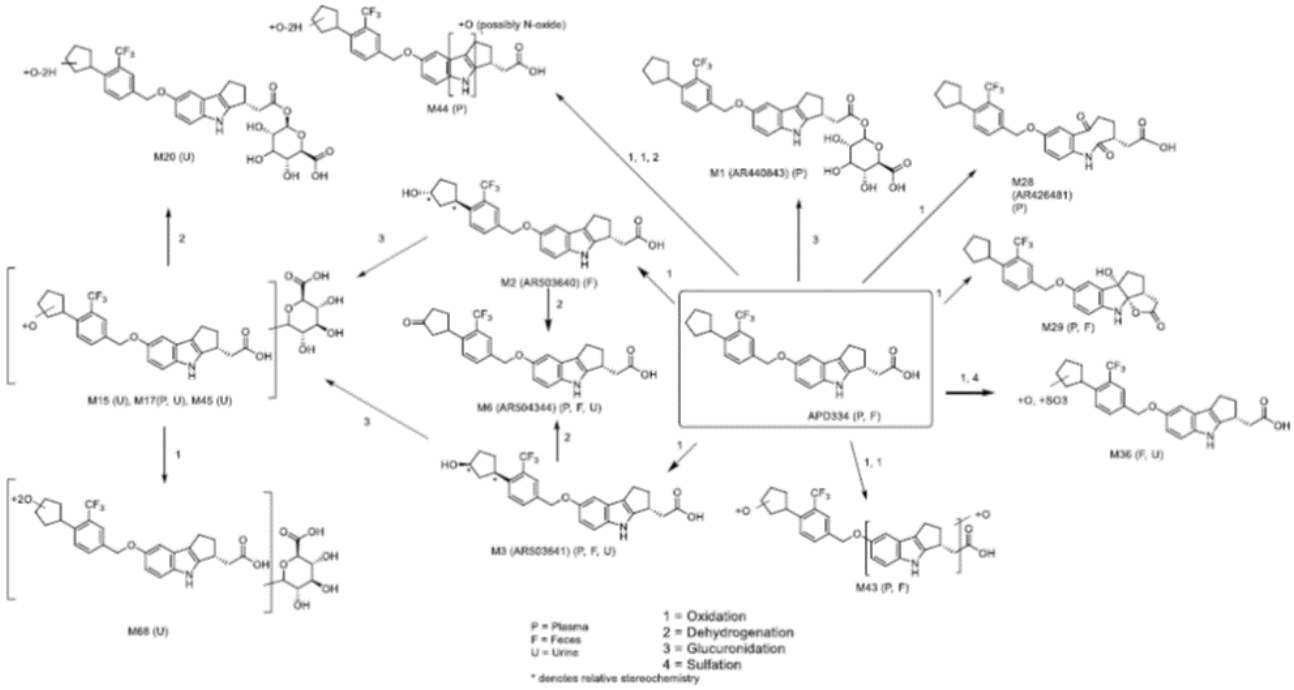
Study (single dose)	Dose	n	PK sampling duration (h)	Terminal $t_{1/2}$ (h) [mean (SD)]	Effective Mean $t_{1/2}$ (h)
			Single-Dose Studies		
APD334-001	0.1 mg	6	144	37.4(5.6)	--
	0.35 mg	6	144	30.7 (2.7)	--
	1 mg	6	144	32.8 (5.0)	--
	3 mg	6	144	35.0 (5.8)	--
	5 mg	6	144	33.8 (2.3)	--
ADP334-007	2mg capsule fasted	14	120	36.7 (12.9)	--
	2 mg tablet fasted	14	120	29.3 (4.28)	--
	2 mg tablet fed	14	120	31.5 (4.90)	--
APD334-008	2.0 mg	30		--	27.3
ADP334-009	1 mg	18	168	42.5 (7.64)	29
	1 mg	18	168	45.6 (7.22)	31
	2 mg	17	168	41.1 (8.07)	30
APD334-108	2 mg Healthy mild	8	504	43.9 (14.9)	30
	2 mg Healthy moderate	8	504	49.0 (16.6)	29
	2 mg Healthy severe	8	504	59.5 (14.8)	32
APD334-112	2 mg Healthy	8	336	52.0 (19.4)	24
APD334-114	2 mg clin tablet fasted	16	168	35.9 (5.64)	30
	2 mg comm tablet fasted	15	168	35.3 (7.20)	30
	2 mg comm tablet fed	16	168	36.6 (7.00)	31
APD334-115	2 mg IR fasted	21	168	31.7 (5.14)	27
APD334-116	1 mg tablet	18	216	38.7 (10.6)	30
ES100101	1 mg	9	144	30.3 (3.84)	28.7
	2 mg	9	144	28.1 (1.81)	27.3
		Overall Mean (h)		**38.1**	**29.4**
		SD		**7.63**	**2.07**
Study (multiple dose)	**Dose (mg)**	**N**	**PK sampling duration (h)**	**t1/2 (h) [mean (SD)]**	**Effective Mean t1/2 (h)**
APD334-002	0.7 mg	9-10	48, +168	45.1 (9.14)	36
	1.35 mg	9-10	48, +168	42.6 (3.71)	30
	2 mg	9-10	48, +168	46.4 (7.81)	36
APD334-109	1 mg Japanese	10	168	40.1 (6.39)	27
	1 mg Caucasian	10	168	36.4 (6.78)	26
	2 mg Japanese	10	168	39.4 (5.09)	29
	2 mg Caucasian	10	168	41.7 (9.14)	33
ES100101	1 mg Chinese	9	144	38.1 (3.31)	32
	2 mg Chinese	9	144	33.3 (2.72)	35
	3 mg Chinese	8	144	37.1 (5.49)	ND
		Overall Mean (h)		**40.0**	**31.2**
		SD		**3.83**	**3.67**

Note: PK data reported from fasted state unless otherwise noted.
Effective half-life determined using the following equation: Effective half-life = ln2 *tau/ ln[Rc-1)/Rc], where Rc is the accumulation ratio determined as AUC∞/AUC0-24 for single dose. The overall mean (SD) determine in the table was calculated manually by summing the individual mean and dividing by the number of studies and SD was determined by the square root of variance by determining each data point's deviation relative to the mean.
[Source: Summary Clinical Pharmacology Table 52 (Study APD334-001 CSR Table 14.2.1.3, Study APD334-007 CSR Table 14.2.4 to 14.2.6, Study APD334-009 CSR Table 14.2.2.1, Study APD334-107 CSR,Table 14.2.1-1, Study ADP334-108 CSR Tables 14.2.2-1.1, and 14.2.2-1.2 to 14.2.2-1.3, Study APD334-112 CSR Table 14.2.2.1, Study APD334-114 CSR Table 14.2.2, Study APD334-115 CSR Table 14.2.2.0, Study APD334-116 CSR Table 14.2.2.1 and Study ES100101 CSR Table 14.4.2.2) and Table 53 (Study APD334-002 CSR Table 14.2.2.1, Study APD334-109 CSR Table 14.2.2.4 and Study ES100101 CSR Table 14.4.2.2).]

Etrasimod was cleared slowly, but was extensively metabolised in humans, indicating elimination of etrasimod occurs primarily by metabolic clearance mechanisms. Based on *in vitro* data, etrasimod is primarily metabolised by CYP2C8 (38%), CYP2C9 (37%) and CYP3A4 (22%), a finding consistent with results from *in vivo* DDI studies (see chapter PK interaction studies below), and to a lesser extent by CYP2C19 and CYP2J2 (1% each), with also direct and/or secondary conjugation by UGTs and sulfotransferases.

In vivo, etrasimod and a total of 19 metabolites (resulting from oxidation of etrasimod, along with dehydrogenation and conjugation) were identified in human plasma pools obtained from multiple-dose up-titration of etrasimod from 2 to 4 mg, based on LC-MS analysis (APD334-008). Further,

[^{14}C]etrasimod human mass balance study APD334-107 revealed extensive metabolism via oxidation, dehydrogenation, glucuronidation, sulfation and a combination of these reactions. In the mass balance study, a total of 11, 21, and 9 metabolites were detected in plasma, urine and faeces, respectively, of these observed metabolites, 14 were identified (Figure 4).



[Source: APD334-107 CSR Appendix 16.2.5.4 Metabolite Profiling and Identification Report, Figure 26]

Figure 4: Proposed biotransformation pathways of APD334 in humans (APD334-107)

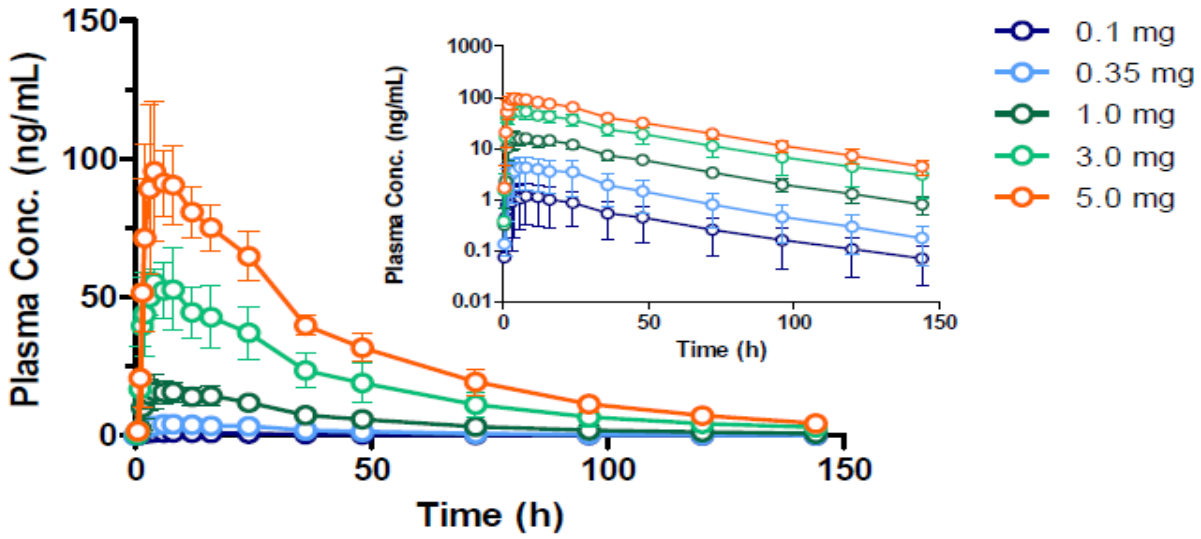
Etrasimod was the major circulating component in human plasma (49% of total radioactivity). The most abundant circulating metabolites across all subjects were hydroxyl metabolite M3 (AR503641) and ketone metabolite M6 (AR504344) contributing 8 to 18% and 10% to 14% of total radioactivity exposure in AUC0-168h subject pools, and 8.27% and 8.54% of total radioactivity exposure in an AUC0-312h cross subject pool.

Etrasimod does not appear to undergo any *in vivo* stereoconversion to its opposite enantiomer. No quantifiable AR401967 was detected in cross-subject pooled plasma samples from patients with UC.

Dose proportionality and time dependencies

Etrasimod exposure measures (Cmax and AUC) increased approximately dose proportional manner over a single dose range from 0.1 to 5 mg (Figure 5, *Table 10*,

Table 11), but increased somewhat greater than dose proportional after multiple (21 days of) daily dosing (Cmax and AUC0-24). The final population PK model was consistent with approximate dose proportionality of etrasimod exposure measures across the entire evaluated single (0.1-5 mg) and multiple (0.25-4 mg once daily) dose range of etrasimod.



Mean ± SD, N=6 per treatment group. [Source: APD334-001 CSR Table 14.2.1.1]

Summaries of single-dose etrasimod plasma PK parameters by treatment group are given in *Table 10*.

Figure 5: Mean (± SD) Plasma Concentration-Time Profiles of Orally Administered Etrasimod (PIC) (SAD Study APD334-001)

Table 10: Summary of Mean Plasma PK Parameters of Etrasimod by Treatment Group (SAD Study APD334-001)

Pharmacokinetic Parameter	**Etrasimod 0.1 mg (N=6)**	**Etrasimod 0.35 mg (N=6)**	**Etrasimod 1 mg (N=6)**	**Etrasimod 3 mg (N=6)**	**Etrasimod 5 mg (N=6)**
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Cmax (ng/mL)	1.73 (0.61)	6.28 (0.36)	17.2 (5.5)	60.5 (11.7)	102 (19)
Tmax (h)[a]	6.00 (4.00-12.00)	7.00 (1.50-24.0)	6.00 (2.00-8.00)	3.50 (1.50-8.00)	4.00 (3.00-6.00)
T1/2z (h)	37.4 (5.6)	30.7 (2.7)	32.8 (5.0)	35.0 (5.8)	33.8 (2.3)
AUC0-144 (ng h/mL)	74.8 (20.4)	257 (27)	753 (157)	2440 (700)	4170 (550)
AUC0-∞ (ng h/mL)	79.8 (21.3)	268 (31)	793 (168)	2600 (840)	4390 (610)
CL/F (L/h)	1.33 (0.37)	1.32 (0.15)	1.30 (0.25)	1.23 (0.29)	1.16 (0.15)
MRT (h)	40.8 (3.4)	37.6 (2.5)	39.5 (3.5)	39.1 (4.5)	39.4 (3.9)
VZ/F (L)	73.4 (29.2)	58.2 (3.5)	61.2 (11.9)	60.3 (9.5)	56.2 (6.7)

[a] Tmax = median (min-max) [Source: APD334-001 CSR Table 14.2.1.3]

Table 11: Assessment of Dose Proportionality of Etrasimod in SAD Study APD334-001

Pharmacokinetic Parameter	**Estimate (90% CI)[a]**
Cmax	1.050 (1.001, 1.099)
AUC0-144	1.033 (0.991, 1.075)
AUC0-inf	1.032 (0.988, 1.075)

a Values are from a linear regression model of the log-transformed data.
[Source: APD334-001 CSR Table 5 (W:\Biostatistics\APD334\001\CSR\pgmanalysis\pk_reg_doseprop.sas; 12:19 14OCT2013)]

Table 12: Summary of Mean (SD) Plasma PK Parameters of APD334 on Days 1 and 21 and accumulation ratio based on Cmax Day 21/Day 1 and AUC0-24Day 21/Day 1 for Cohorts 1, 2, and 3 (MAD Study APD334-002, Addendum PK report Version Final V1.0)

Pharmacokinetic Parameter		**APD334**		
		Cohort 1 0.7 mg (N=10) Mean (SD)	**Cohort 2 1.35 mg (N=10) Mean (SD)**	**Cohort 3 2.0 mg (N=10) Mean (SD)**
Day 1	t_{max} (h)[a]	8.00 (3.08-12.0)	6.00 (2.00-8.00)	8.00 (2.00-12.0)
	C_{max} (ng/mL)	12.9 (2.84)	29.2 (8.37)	43.8 (12.9)
	AUC_{last} (ng·h/mL)	224 (51.2)	493 (100)	746 (196)
	AUC_{0-24} (ng·h/mL)	240 (45.7)[b]	496 (101)	785 (177)[b]
Day 21	λZ (1/h)	0.01587 (0.01562)	0.01639 (0.01634)	0.01531 (0.01511)
	$t_{1/2}$ (h)	45.1 (9.14)	42.6 (3.71)[c]	46.4 (7.81)
	t_{max} (h)[a]	8.00 (1.00-8.00)	8.00 (2.00-8.00)[c]	8.00 (2.00-8.00)
	C_{max} (ng/mL)	30.8 (6.61)	63.5 (11.8)[c]	113 (27.5)
	AUC_{last} (ng·h/mL)	1665 (597)	3092 (667)[c]	5976 (1578)
	AUC_{0-inf} (ng·h/mL)	1834 (754)	3326 (742)[c]	6544 (1850)
	V_Z/F (L)	77.3 (12.2)	70.9 (10.7)[c]	66.2 (12.0)
	CL_{ss}/F (L/h)	1.22 (0.241)	1.16 (0.218)[c]	0.977 (0.266)
	MRT_{inf} (h)	59.4 (15.6)	53.7 (5.43)[c]	60.3 (0.9)
	C_{trough} (ng/mL)	20.2 (4.72)	40.3 (8.21)[c]	71.8 (16.5)
	$C_{avg,ss}$ (ng/mL)	24.8 (5.06)	49.8 (9.40)[c]	90.1 (20.3)
	AUC_{0-24} (ng·h/mL)	596 (122)	1197 (226)[c]	2163 (489)
	$t_{1/2eff}$ (h)	35.1 (8.64)[b]	29.7 (29.5)[c]	36.4 (7.66)[b]
Rac	C_{max} D21/D1	2.42 (0.421)	2.12 (0.284)[c]	2.72 (0.934)
	AUC_{0-24} D21/D1	2.65 (0.512)[b]	2.33 (0.214)[c]	2.73 (0.454)[b]

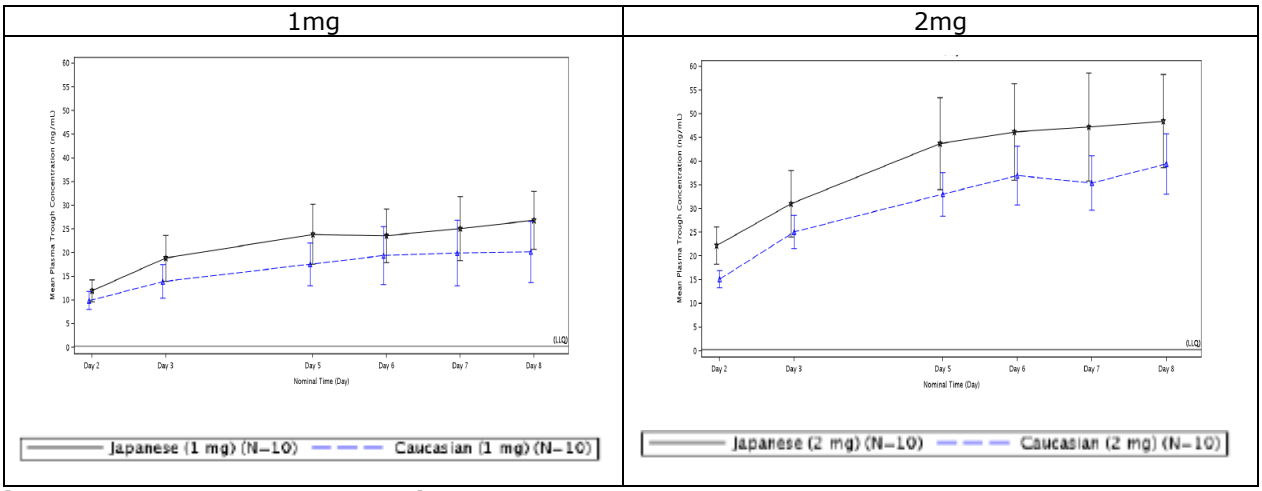
a Median (min-max)
b N=8 (in cohort 1 and 3 not determined in 2 subjects each due to Tlast <24 hr and could not extrapolate)
c N=9 (subject 66 withdrew consent prior to Day 21 and contributed only to Day 1 PK parameters)
[Source: APD334-002 report body addendum (Addendum PK report Version Final V1.0, Figure 14.2.1a), Table 5.1]*
*Note: amended from source by Assessor based on actual number of subjects contributing to PK parameters according to Tables 14.2.3.7a, 14.2.3.8a and 14.2.3.9a

Table 13: Etrasimod Dose Proportionality Assessment (Cohort 1-3) after single (Day 1) and multiple (Day 21) dose administration (MAD Study APD334-002)

Pharmacokinetic Parameter	**Slope**	**90% CI slope**
Day 1		
C_{max}	1.15	0.96, 1.34
AUC_{0-24}	1.12	0.95, 1.29
Day 21		
C_{max}	1.22	1.06, 1.38
AUC_{0-24}	1.21	1.05, 1.36
AUC_{inf}	1.21	0.99, 1.43

[Source: APD334-002 report body addendum (Addendum PK report Version Final V1.0, Figure 14.2.1a), Table 5.4]*
*NOTE: In APD334-002 CSR Table 14.2.4, slope estimate (90% CI) values from a linear regression model of the log-transformed data (as described in CSR 9.7.1.2) were presented with different outcome, presumably due to use of nominal times rather than actual sampling times]

Following multiple-dose administration of etrasimod, steady-state for etrasimod exposure measures (Cmax, AUC0-24, Ctrough) were reached within 7 days of dosing in healthy subjects (APD334-109).



[APD334-109 CSR Source: Figures 14.2.1.5]

Figure 6: Mean (SD) Trough Plasma Etrasimod Concentration-Time Profiles Following Administration of Etrasimod to Healthy Japanese and Caucasian Adult Male Subjects (Left = 1 mg; Right = 2 mg) (Linear Scale) (APD334-109)

Accumulation index values for both peak (Cmax) and total (AUC0-24) plasma exposure measures for etrasimod ranged from about 2- to 3 -fold in healthy subjects with once daily dosing of etrasimod.

Following multiple dose administration of 1 mg and 2 mg etrasimod qd in healthy Chinese subjects, the temporal change parameter (TCP) calculated as Day 17 AUC0 τ / Day 1 AUC0-inf was 1.07 and 1.14, suggesting that PK of etrasimod is not time-dependent.

The range of intrasubject variabilities (%CV) for etrasimod Cmax (8.0-10.7%), AUC0-last (5.1-6.4%), and AUC0-∞ (5.4-7.0%) values were low between etrasimod 2 mg IR formulations (clinical and commercial) given in the fasted state or between fed and fasted states
Inter-subject variability (%CV) for single and multiple-dose etrasimod Cmax and AUC measures was low-to-moderate ranging from 12 to 37% and 16 to 44%, respectively in Phase 1 studies.
In patients with UC, inter-subject variability (gCV) for etrasimod Cavg trough, ss values was moderate (47.80% in APD334-301).

Special populations

Target window

Etrasimod Exposures Following 2 mg QD

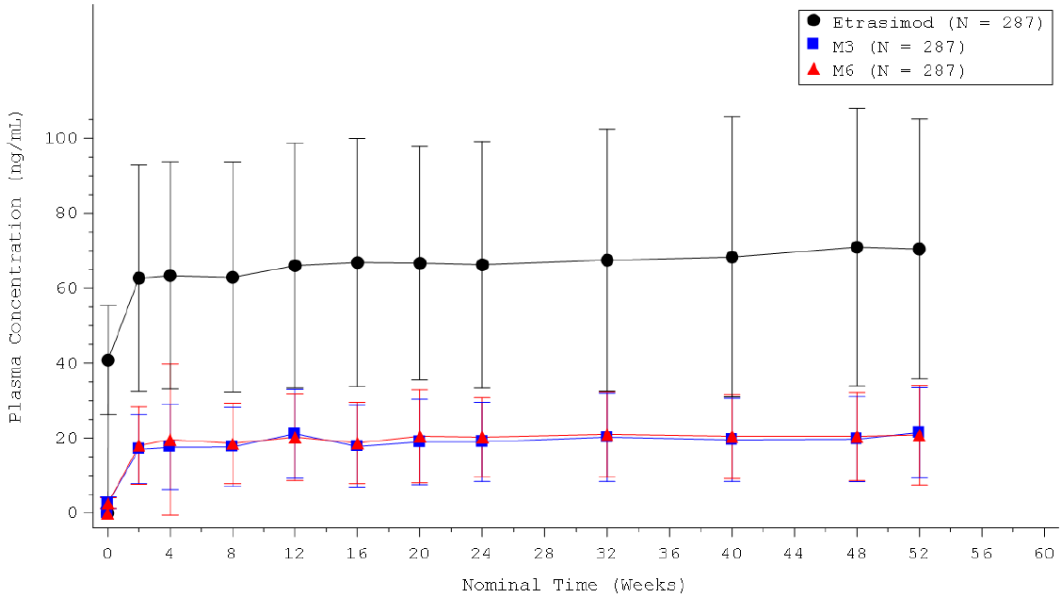
Etrasimod population PK analyses were conducted using data pooled from multiple clinical studies (ARE0301H-PopPK Report). Median post-hoc individual steady state AUCss estimates after etrasimod 2 mg in the UC pivotal Phase 3 Studies APD334-301 and APD334-302 was 2010 ng*hr/mL (95% PI: 1168 – 3489 (median: 2.5 to 97.5%).

Interindividual variability (IIV) was, in general, low to moderate for etrasimod exposure metrics estimates, from the population PK analysis CV of 26.6% (ARE0301H-PopPK Report); this is consistent with interparticipant variability estimates of AUC from several Phase 1 studies that ranged from 16 to 44%, where intraparticipant variability estimates were also low.

Target population

In patients with UC, etrasimod PK was not determined by noncompartmental analysis due to sparse sampling. With etrasimod 2 mg once daily dosing for 52 weeks in APD334-301, mean steady-state (predose) trough concentrations (Ctrough,ss) for etrasimod were achieved by Week 2 and maintained to the end of treatment at Week 52, with geometric mean (geometric %CV) ranging from 56.22 (55.17) to 63.91 (56.83) ng/mL (Figure 7) . The mean plasma concentrations for M3 and M6 overlap

across all visits and were just below 30% of those observed for etrasimod in APD334-301. The overall geometric mean Cavg trough, ss value (designated as average steady-state Ctrough, ss, W2-W52 in the CSR) was 58.38 ng/mL, 16.24 ng/mL and 16.72 ng/mL for etrasimod, M3 and M6, respectively. Between-subject variability (gCV) for Cavg trough, ss values was 47.8%, 57.99 and 59.78% for etrasimod, M3 and M6, respectively.



Note: Mean concentrations that are less than the lower limit of quantification (Etrasimod: 0.250 ng/mL; M3 and M6: 0.150 ng/mL)) are presented as zero.
Day 1 is 4 hours postdose and all other times represent predose trough concentration occurring within 24 hours (± 8 hours) of the previous dose. [Source APD334-301 CSR, Figure 14.2.55.2]

Figure 7: Overlay of Mean (±SD) Etrasimod, M3, and M6 Plasma Concentration-time Profiles by Treatment on Linear Scales (Weeks 0 to 52) (PK Set, APD334-301)

Renal Impairment

Although the renal clearance of unchanged etrasimod is negligible, with the 4.89% of total radiocarbon recovered from urine divided among multiple metabolites, renal impairment can influence hepatic metabolism and transport of drugs. Therefore, a dedicated single dose etrasimod reduced design renal impairment PK study was conducted in 8 subjects with severe renal impairment or ESRD, together specified as eGFR ≤ 29 mL/min, regardless of dialysis, compared to a matched normal kidney function group. The renal impaired subject group did not comply with guideline recommendations, being a mixed group of 2 severe renal impaired subjects based on eGFR as determined by the MDRD equation of 27 and 24.7 mL/min at screening and 6 subjects with ESRD (eGFR between 7.6 and 13.3 mL/min at screening) requiring dialysis. Following a single oral dose of 2mg etrasimod, no or only modest changes in PK of both etrasimod and of unbound etrasimod were apparent between the groups, with slight decreases in exposure parameters (*Table 17*) rather than increases as predicted from popPK. Etrasimod has not been studied to assess the effect of haemodialysis on PK but was considered unlikely to be affected based on high protein binding in plasma (97.9%).

Table 14: Statistical Analysis of the Effect of Renal Impairment on the PK Parameters of Etrasimod (PK Set, APD334-112)

PK Parameter (Unit)	Comparison	Severe		Normal		GLSM Ratio (%) T:R	90% CI for GLSM Ratio
		n	GLSM (90% CI)	n	GLSM (90% CI)		
Cmax (ng/mL)	Severe:Normal	8	29.06 (25.71, 32.85)	8	35.67 (31.55, 40.32)	81.49	(68.42, 97.05)
AUClast (h*ng/mL)	Severe:Normal	8	1357 (1067, 1724)	8	1542 (1213, 1959)	88.00	(62.53, 123.84)
AUCinf (h*ng/mL)	Severe:Normal	8	1409 (1111, 1787)	8	1592 (1256, 2019)	88.48	(63.06, 124.14)

R, reference (normal renal function); T, test (severe renal impairment = severe impairment and/or ESRD).
Note: Severe Renal Impairment = severe impairment and/or end-stage renal disease (estimated glomerular filtration rate ≤ 29 mL/min; either requiring haemodialysis or not). The log-transformed PK parameter was used for the analysis of covariance, with renal function as the fixed effect. Baseline age and weight were included as covariate in the model.

The PK of the metabolites M3 and M6 was significantly changed. Based on analysis of covariance, with renal function as the fixed effect and baseline age and weight included as covariate, Cmax, AUClast, and AUCinf were 48%, 54%, and 43% lower for M3 and 30%, 37%, and 26% lower for M6, respectively, in the severe renal impairment group compared to matched normal renal function control group. Metabolic ratio was also reduced from 0.24 to 0.15 for M3 and from 0.21 to 0.17 for M6.

Hepatic impairment

Etrasimod is primarily metabolised and eliminated by the liver, therefore it is expected that hepatic impairment would have an impact on etrasimod PK.
A dedicated single dose etrasimod hepatic impairment PK study was conducted to evaluate the effect of hepatic impairment on the plasma PK of etrasimod, M3 and M6 and unbound etrasimod in subjects with mild (Child-Pugh Grade A), moderate (Child-Pugh Grade B) and severe (Child-Pugh Grade C) hepatic impairment compared to their respective matched (age, sex, and BMI) normal liver function group. While the mean geometric Cmax values were similar between groups, the geometric mean AUC0-∞ increased by 13%, 29% and 57% in subjects in the mild, moderate and severe hepatic impairment group compared to the respective normal matched liver function group (*Table 15*).

Table 15: Statistical Parametric Analysis of the Effect of Hepatic Impairment on Etrasimod Exposure PK Parameters (APD334-108)

Parameter	Comparison (Test vs. Ref)[e]	Test		Reference		Geo LS Mean Ratio (Test:Ref)[c] (%)	90% CI[d] (%)	P-value
		n[a]	Geo LS Mean (90% CI)[b]	n[a]	Geo LS Mean (90% CI)[b]			
C_{max} (ng/mL)	Mild vs Normal	8	33.5 (30.5, 36.9)	8	33.0 (29.9, 36.5)	101.6	88.4, 116.9	0.8395
	Moderate vs Normal	8	31.3 (28.2, 34.8)	8	34.0 (30.6, 37.6)	92.3	80.0, 106.6	0.3415
	Severe vs Normal	6	41.7 (35.6, 48.9)	6	40.0 (34.2, 46.8)	104.3	84.4, 128.9	0.7194
AUC_{0-t} (h*ng/mL)	Mild vs Normal	8	1440 (1260, 1660)	8	1270 (1100, 1470)	113.3	94.9, 135.3	0.2290
	Moderate vs Normal	8	1720 (1520, 1950)	8	1330 (1180, 1510)	129.1	108.6, 153.3	0.0216
	Severe vs Normal	4	2310 (1500, 3580)	4	1600 (1040, 2470)	144.7	91.8, 228.1	0.1492
$AUC_{0-\infty}$ (h*ng/mL)	Mild vs Normal	8	1490 (1300, 1710)	8	1320 (1140, 1530)	112.9	94.1, 135.5	0.2523
	Moderate vs Normal	8	1770 (1570, 2010)	8	1380 (1220, 1550)	128.9	108.6, 153.0	0.0216
	Severe vs Normal	6	2710 (2160, 3410)	6	1730 (1380, 2160)	157.3	122.0, 202.8	0.0164

[a] n = the number of subjects in each group used in the model.
[b] LS means for AUC0-t, AUC0-∞ and Cmax, calculated by transforming the ln log means to linear scale.
[c] Ratio of LS means for ln log-transformed AUC0-t, AUC0-∞ and percent Cmax, ln log-transformed to linear scale.
[d] The 90% CI for ratio of LS means of ln log-transformed AUC0-t, AUC0-∞ and % Cmax, ln log transformed back to the linear scale.
[e] Due to potential underestimation of AUC0-t, two severe impairment subjects (and their normal matched subjects) were excluded from the statistical comparison of severe hepatic impairment versus normal hepatic function for AUC0-t.
Note: Log (PK parameter) = sex + bodyweight + hepatic function group + random error.
[Source: APD334-108 CSR Table 14.2.2-6.1]

Exposures of metabolites M3 and M6 were found significantly changed in a disproportional manner as compared to etrasimod, in the following exemplified for AUC measures which increased 1.6 fold, 1.9

fold and 3 fold for M3 and 2 fold, 1.74 fold and 1.93 fold for M6, compared to 1.1 fold, 1.3 fold and 1.57 fold for etrasimod, in mild, moderate and severe hepatic impairment groups compared to their normal hepatic control groups, respectively. MR was increased accordingly for both M3 and M6, and mean t1/2 generally prolonged, ranging in mild and moderate hepatic impairment groups as high as 72h for M3 and 82 h for M6 (compared to 59h for M3 and 57 h for M6 in matched normal groups).

When relationship between PK parameters and Child-Pugh classification parameters for etrasimod was evaluated, results indicated a moderate negative correlation between CL/F and each of the covariates CP score, total bilirubin, and prothrombin INR, while the correlation between CL/F and serum albumin was moderate and positive.

Gender

Regarding gender, higher exposures to etrasimod were noticed in females compared to males with the differences being mainly attributed to body-weight.

Race

In a Japanese Caucasian bridging study, differences in PK between the two ethnic groups were attributed to body-weight. Results from a PK study in Chinese subjects appear generally comparable based on cross study comparison. Information regarding race and ethnicity other than Caucasian, Japanese and Chinese from noncompartmental analysis is missing.

Based on population PK modelling, ethnicity, race, and tobacco use should not have a significant impact on etrasimod exposure.

Weight

Weight was a significant covariate in population PK modelling. Model-predicted etrasimod exposure for subjects < 40 kg was 1.5-fold higher than exposure of typical 70 kg subject. The target population also includes patients ≥ 16 years in whom such low weights may occur more frequently. Since the argumentation relies mainly on modelling, observed data for lymphocyte counts and the events qualified as ADRs were submitted for the patients of the lowest weight group. No weight related trends regarding safety endpoints were observed. A statement that a 1.5-fold higher exposure in patients of body weight <40 kg is predicted is included in the SmPC. Based on Pop PK analysis, sex, race, ethnicity and age had a minimal impact on etrasimod exposure. It is agreed that no dose adjustment based on these covariates is necessary.

Age

No PK information is available regarding elderly and adolescents from Phase 1 studies.

In Phase 2 and 3 studies, based on a very limited number of patients aged ≥65 <74, there did not appear to be a relationship between etrasimod Cavg trough, ss and older age.

The number of subjects and the proportion of subjects that were included in the population PK analysis for different thresholds is provided below. The population PK model used a total of 1079 subjects from 18 studies that included healthy volunteers or patients with moderate to severely active ulcerative colitis.

Age Group	**Count**	**Percentage**
All Subjects	1079	100
Less than 50	828	76.7

50 and Older	251	23.3
60 and Older	98	9.1
65 and Older	40	3.7
70 and older	15	1.4

1. Source: improve artifact ID: FI-41717806
The cumulative counts and percentages, based on decreasing age, are provided for each of the age thresholds. These following studies were included in the analysis dataset: APD334-001, APD334-002, APD334-003, APD334-007, APD334-008, APD334-009, APD334-107, APD334-108, APD334-109, APD334-110, APD334-111, APD334-112, APD334-114, APD334-115, APD334-116, APD334-301, APD334-302, and ES101001.

Data on adolescent patients was too sparse with only 1 patient contributing to PK.

From population PK modelling, no significant differences in etrasimod PK are expected between adults and older adolescent patients (age 16 to < 18 years) with UC. Nevertheless, PKPD modelling for lymphocyte responses predicted slightly lower lymphocyte counts in older adolescents, with a slightly larger reduction from baseline and slightly slower return to baseline values compared to adults (see also section on weight above).

Pharmacokinetic interaction studies

A series of *in vitro* metabolism studies showed oxidative metabolism of etrasimod by CYP2C8 (38%), CYP2C9 (37%) and CYP3A4 (22%) with minor contributions from CYP2C19 and CYP2J2 (1%).

To address clinical drug interactions mediated by CYP2C8, CYP2C9 and CYP3A4, clinical DDI studies were conducted with fluconazole (a moderate inhibitor of CYP2C9 and CYP3A4, and a strong inhibitor of CYP2C19), gemfibrozil (a strong inhibitor of CYP2C8), itraconazole (a strong inhibitor of CYP3A4) and rifampin (a strong inducer of CYP3A4 and CYP2C19, and a moderate inducer of CYP2C8 and CYP2C9) as potential perpetrators of a drug interaction with etrasimod as a victim drug.

Inhibitors of CYP: All three CYP inhibitors tested generally caused increases in etrasimod, M3 and M6 plasma exposure. As fluconazole inhibits multiple CYPs involved in etrasimod disposition, plasma exposure increases were most prominent (up to 1.84 fold) and considered clinically relevant by the applicant. Co-administration of etrasimod with a therapeutic agent or a combination of agents that are moderate to strong inhibitors of two or more of the following CYP enzymes (CYP2C8, CYP2C9, and CYP3A4) (e.g., fluconazole) increases the exposure of etrasimod and is not recommended in the SmPC.

Inducers of CYP: Upon coadministration with rifampin (a strong inducer of CYP3A4 and CYP2C19, and a moderate inducer of CYP2C8 and CYP2C9) etrasimod exposure decreased by 49% (AUC∞) and Cmax increased by 24%. All the enzymes induced by rifampin contribute to the oxidative metabolism of etrasimod. Co-administration of etrasimod with a therapeutic agent or a combination of agents that are moderate to strong inducers of two or more of the following CYP enzymes (CYP2C8, CYP2C9, and CYP3A4) (e.g., rifampicin, enzalutamide) decreases the exposure of etrasimod and is not recommended in the SmPC.

Effect of CYP2C9 polymorphism

Due to the risk of increased exposure of etrasimod, co-administration of etrasimod in patients who are CYP2C9 poor metabolisers (<5% of the population) and who take medicinal products that are moderate or strong inhibitors of CYP2C8 and/or CYP3A4 is not recommended in the SmPC.

Oral Contraception (EE/LVG): Coadministration with etrasimod caused 24% increase in EE following once daily repeated dosing, not considered clinically relevant by the applicant. The information about the 24% observed increase in EE has been included in the etrasimod PI, in line with the PI of other medicinal products causing increases of similar magnitude.

Acid-Reducing Agents: No study has been conducted. Etrasimod is a weak-acid drug and is dosed as an IR formulation. From the FDA guidance, the magnitude of pH-dependent DDIs for weak-acid drugs

is generally modest and the need to conduct such study is dependent on the safety profile (FDA 2020a). The absorption of etrasimod is nearly intact based on data from human mass balance study in which plasma Cmax of etrasimod and plasma Cmax of total radioactivity were nearly similar. A gastric pH-dependent (ARA) DDI study [using antacids, histamine (H2)-receptor antagonists (H2 blockers), and/or proton pump inhibitors (PPIs)] was not considered necessary or conducted. According to the applicant there is no expected impact on the safety profile of etrasimod due to any potential ARA interaction as the compound appears to be extensively absorbed unchanged.

Pharmacokinetics using human biomaterials

Etrasimod as substrate of UGT: An *in vitro* study with human recombinant UGT enzymes identified that the etrasimod acyl glucuronide metabolite was formed by UGT1A7, UGT1A1, UGT1A4, and UGT1A9. This was not followed up.

Substrate of Membrane Transporters: Based on *in vitro* experiments, etrasimod does not seem to be a substrate of P-gp, BCRP, OATP1B1 and OATP1B3, OAT1, OAT3, OCT1, or OCT2 transporters. Hence, no clinical DDI studies to investigate the role of these drug transporters in the disposition of etrasimod were considered necessary or conducted.

Metabolising enzymes

Etrasimod as an inhibitor of CYP enzymes: There was little or no direct or time dependent inhibition by etrasimod with any of the CYP enzymes evaluated (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4), with the exception of CYP2C8 which was directly inhibited with an IC50 of 4.0 µM. Based on the basic model, etrasimod exhibits some potential for inhibition of CYP2C8 (R1 = 1.07). To further assess the risk for *in vivo* DDI, the applicant presented additional mechanistic static model AUCR calculation. Based on ka derived from popPK modelling, the risk of clinically meaningful CYP2C8 inhibition may be regarded as low and no further *in vivo* studies were conducted.

Etrasimod as an inducer of CYP enzymes (CYP1A2, CYP2B6 and CYP3A4): In *in vitro* study XT163079, etrasimod at 1 µM and 10 µM showed no induction of CYP1A2 mRNA levels. However, for CYP2B6 and CYP3A4 enzymes, the study was positive since mRNA increased ≥ 2-fold in a dose-dependent manner. Due to limitations in non-guideline conform vitro study XT163079, risk assessment based on calculation of R3 (FDA DDI 2020) and the mechanistic static model were not possible. A further *in vitro* study PF-07915503 was hence conducted (mRNA and activity for CYP1A2, CYP2B6 and CYP3A4, mRNA for CYP2C). Despite several non-guideline conform deficiencies noted regarding design and conduct, the study may still be considered acceptable based on controls. Treatment of human hepatocytes with etrasimod (re-labelled as PF-07915503) to the limits of its solubility and cytotoxicity did not cause an induction response of any CYP enzyme tested. Rather, a concentration dependent decrease was observed on CYP3A4, CYP2B6, CYP1A2 and CYP2C8 at high concentrations of etrasimod which was not likely attributed to a cytotoxic effect. Based on the lack of induction observed, the risk of clinically significant induction of CYP1A2, CYP2B6, CYP3A4 and CYP2C enzymes may be considered low, suggesting that no further studies should be required.

Etrasimod as inhibitor of UGT: In non-guideline conform preliminary study XT165088, etrasimod directly inhibited UGT1A1 and UGT1A6-mediated activities up to 28% and 48%, respectively, at 10 µM. Using the basic model and an estimate for non-specific microsomal binding considered conservative, UGT1A6 R1=1.02 value was calculated, suggesting that a potential systemic inhibition risk cannot be fully excluded for UGT1A6. Less conservatively recalculated UGT1A6 R1 value of 1.005 does not likely indicate a potential DDI UGT1A6 risk. As, based on the applicant's response, the likelihood is low that etrasimod would be concomitantly used with any sensitive UGT1A6 substrates, further studies may be considered dispensable.

Etrasimod as an inhibitor of transporters: Based on *in vitro* studies and evaluation whether a clinical DDI study was required, etrasimod appears unlikely to produce a clinically meaningful inhibition of any membrane transporters tested (i.e. P-gp, BCRP, OATP1B1/3, OAT1/3, OCT1/2, MATE1/2K).

Population PK Modelling

Population PK modelling was used to describe etrasimod PK by a two-compartment model with sequential zero- and first-order absorption and involved modelling of 16,205 etrasimod PK observation measures obtained from a total of 1079 human subjects (411 healthy volunteers and 668 UC patients). Diagnostic plots demonstrated an adequate fit of the final model. Results are shown in ***Table 16*** and Figure 8.

Table 16: Summary of structural parameter estimates for final model

		Estimand	Estimate	95% CI	Bulk ESS	Tail ESS	$\hat{R}$
CL/F	Apparent clearance (L/h)	$\exp(\theta_1)$	1.06	(1.03, 1.09)	4011	3956	1.00
V_2/F	Apparent central volume (L)	$\exp(\theta_2)$	44.8	(44.2, 45.6)	3010	3893	1.00
Q/F	Intercompartmental clearance (L/h)	$\exp(\theta_3)$	0.160	(0.153, 0.168)	970	2008	1.01
V_3/F	Peripheral volume (L)	$\exp(\theta_4)$	25.2	(24.0, 26.4)	1153	2072	1.00
k_a	1st-order absorption rate constant (1/h)	$\exp(\theta_5)$	1.57	(1.43, 1.74)	581	1540	1.00
D_1	0th-order absorption duration (h)	$\exp(\theta_6)$	1.05	(0.962, 1.14)	228	568	1.02

Parameters estimated in the log domains were back-transformed for clarity
Abbreviations: CI = confidence interval; ESS = effective sample size; $\hat{R}$ = Gelman-Rubin diagnostic
Source code: pk-table-400.R
Source file: pk-table-400-struct.tex

To make inferences about potential covariate effects on drug exposure metrics, simulations with 2 mg etrasimod daily were run using multivariate covariate constellations that represented the target population. The colored diamonds represent the median and the solid horizontal lines extending from the diamonds represent the 90% prediction interval (PI). The line segments above the diamonds and ends of each PI represent 95% confidence intervals of the respective quantile. The vertical dot-dash line and grey shaded area are the null value and reference range, defined as the median and 90% PI for the reference population, respectively. Abbreviations: eGFR = estimated glomerular filtration rate.

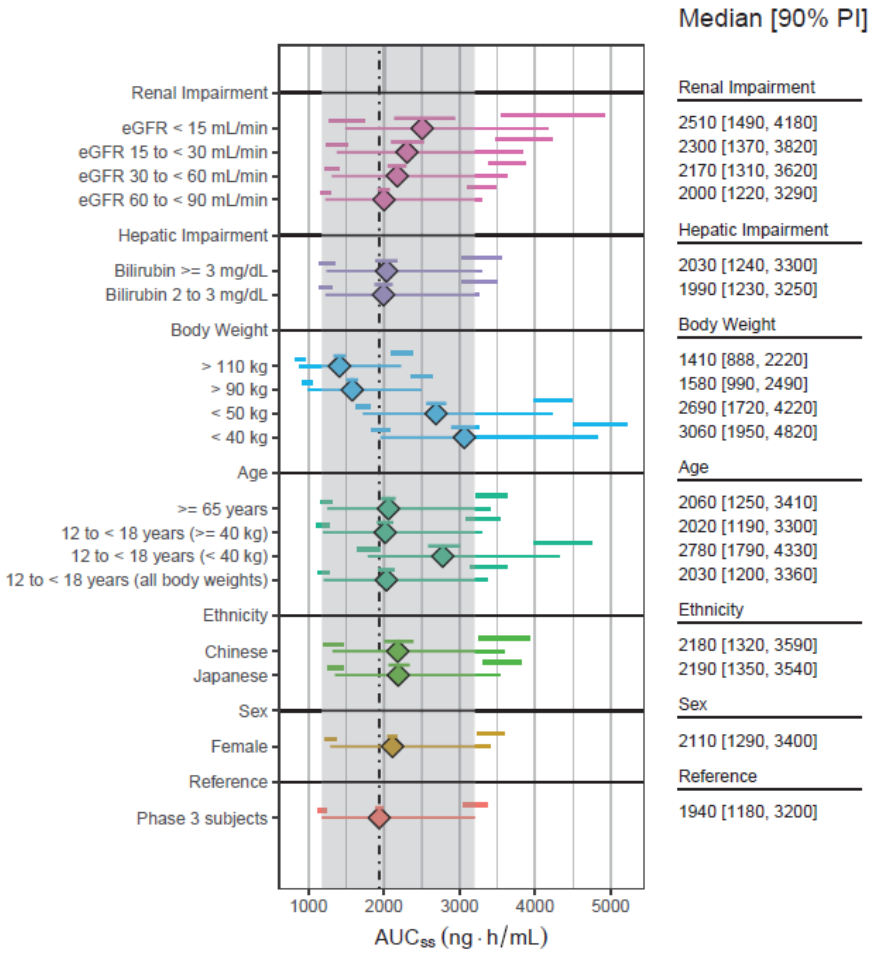


Figure 8: Multivariate forest plot showing covariate effects on the etrasimod AUCss

Plasma clearance was estimated to be 1.06 L/h, apparent volume of distribution after oral dosing at steady state was estimated to be 70.0 L for a 70 kg subject. Predictions of terminal half-life (33.9 h) were much greater than previous estimates using non-compartmental analysis, this might be explained with limited sampling in studies that the NCAs are based on, and in the modelling dataset, also later time points for sampling were available.

Inter-individual variability was low-to-moderate: CL/F (CV=26.6%), V2/F (CV=19.5%) and ka (CV=61.3%). All parameters were estimated with good precision as evidenced by 95%CI ranges. The shrinkage was reasonable: CL/F (4.12%), V2/F (17.5%) and ka (50.1%).

Data handling is overall considered appropriate; there was only 1.3% BLQ values which were excluded from the analysis. Goodness-of-fit plots showed that the model described the data reasonably well. VPCs generally show that the model is able to reproduce both the central trend and variability in the observed data.

The final model included estimated covariate effects for body weight on all clearance and volume terms and additionally contained the effects of age, sex, patient status, ethnicity, race, baseline bilirubin, baseline eGFR, and baseline tobacco use on CL/F, and the effect of formulation on ka, D1, and

bioavailability to the absorption compartment (F1). Inter-individual variability only slightly reduced by including the covariate effects to the base model.

Body weight and renal impairment were found as most influential covariates. However, no implications on dosing were concluded from that. The results regarding renal function and low bodyweight should be interpreted with caution due to the low number of cases with body weight lower than 50 kg (n=30, no data for body weight < 40 kg) and with eGFR <30 mL/min (n=9). For interpreting the results for patients with hepatic impairment, it should be highlighted that no data of metabolite concentrations were used in model development and patient numbers are small (n=7).

A Modelling and Simulation Plan was not embedded in the report and was submitted subsequently. It was justified why the Bayes estimation method was used and that this decision was predefined. It was discussed whether a more standard estimation approach could lead to a simpler model using less covariates, which might be of comparable informative value, but the current model was preferred. Results of population PK modelling were further used for lymphocyte model development and modelling PK and response in adolescents (16-18 years of age).

2.6.2.2. Pharmacodynamics

Mechanism of action

Etrasimod has been characterised as a selective S1P modulator with a preference for the S1P1, 4, and 5 receptors. S1P modulation as such is not a new pharmacological principle, because there are already 4 other substances currently licensed on the EU market, one of which is also licensed for the indication claimed for etrasimod. Etrasimod is claimed to possess a balanced S1P1 agonism between G protein activation and β-arrestin recruitment. At the molecular level, upon binding to S1P1, the substance acts as functional antagonist by inducing and sustaining receptor internalisation. This internalisation partially and reversibly blocks the capacity of lymphocytes to egress from lymphoid organs.

The primary mechanism of action results in a blockage of lymphocytes within the lymphoid organs, which becomes obvious with the reduction of lymphocytes in the peripheral blood.

S1P – among others – is also involved in the regulation of heart rate. All S1P receptor modulators have demonstrated a mostly transient, first dose associated chronotropic and dromotropic effect which are usually dose-dependent.

In consequence, the applicant has concentrated the documentation and exploration of the pharmacodynamics of the compound on these two expected effects, one of which transports the desired anti-inflammatory activity, while the heart-rate reduction can be classified as adverse.

Primary and Secondary pharmacology

Effects on peripheral lymphocyte counts:

The effects on peripheral lymphocyte counts have been evaluated in almost all phase I, phase II, as well as in phase III studies as part of the routine haematology safety evaluation. However, dedicated studies for the exploration of lymphocyte reducing effects have been the studies APD334-001, APD334-002, APD334-109, and ES100101 which were all conducted in healthy volunteers. The full exploration of the effects in healthy volunteers and further documentation of the effects in patients with routine haematology investigations is considered appropriate.

In study APD334-001 which was the single ascending dose early PK study, 5 dose levels between 0.1 mg and 5 mg have been tested. At baseline, all treatment groups had a mean lymphocyte count of just above or slightly below $2.0x10^3$ cells per µl, which was reduced to a nadir around $1.6x10^3$ for the doses

up to 1 mg, and of 0.98, and 0.75, for the two higher dose-groups of 3 mg and 5 mg respectively, indicating a dose-dependent effect. The main results are shown in the following table:

Table 17: Summary of Baseline and Nadir Total Peripheral Blood Lymphocyte Count Assessments by Treatment Group (Study APD334 001)

Treatment	Placebo (N = 10)	Etrasimod 0.1 mg (N = 6)	Etrasimod 0.35 mg (N = 6)	Etrasimod 1 mg (N = 6)	Etrasimod 3 mg (N = 6)	Etrasimod 5 mg (N = 6)
Baseline Lymphocyte Counts (× 10^3/µL)[a]						
Mean (SD)	2.16 (0.50)	2.08 (0.30)	2.01 (0.79)	1.94 (0.38)	1.86 (0.66)	2.05 (0.63)
Nadir Lymphocyte Counts (× 10^3/µL)						
Mean (SD)	1.61 (0.24)	1.68 (0.34)	1.57 (0.52)	1.52 (0.40)	0.98 (0.41)	0.75 (0.34)
% Nadir over Baseline Lymphocyte Counts						
Mean (SE)	75.94 (3.26)	81.24 (4.67)	80.48 (5.24)	77.49 (3.81)	52.47 (2.80)	35.91 (3.17)
Time to Nadir (hours)						
Median min-max	2.00 1.00, 24.00	2.00 1.00, 120.00	2.00 1.00, 24.00	30.00 4.00, 48.00	16.00 4.00, 24.00	6.00 4.00, 24.00

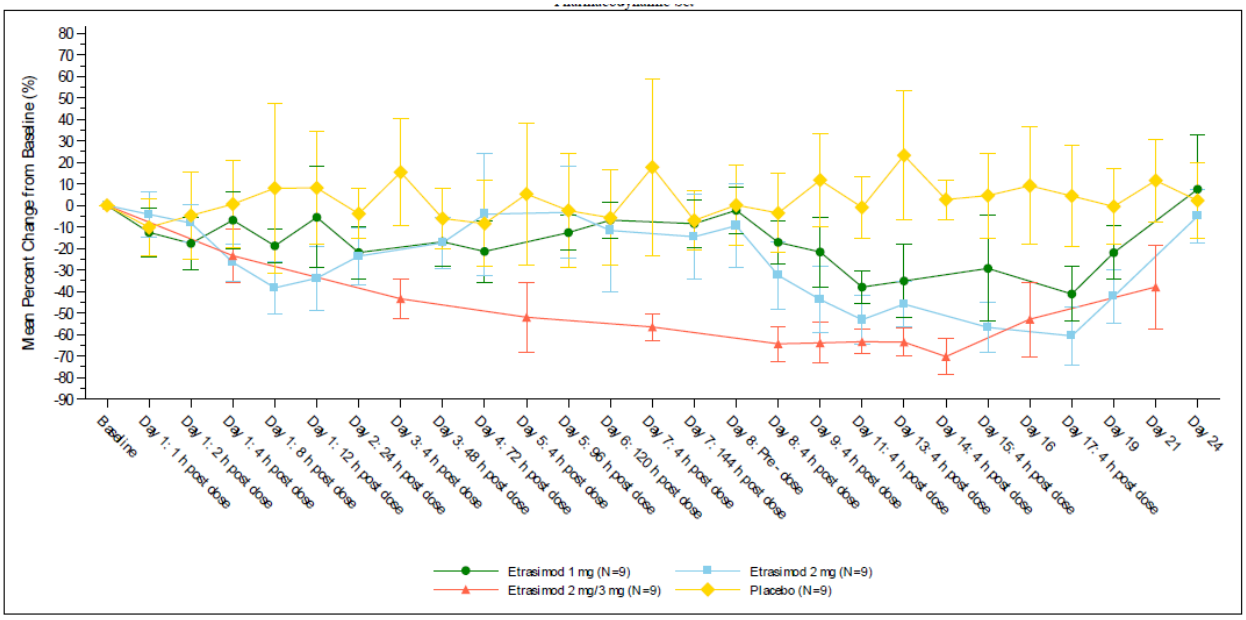
Study APD334-002 was the multiple- and ascending dose PK study using doses of 0.7, 1.35, 2.0, and 3 mg administered for 21 days. The study demonstrated a reduction of baseline lymphocyte counts at day 21 which was partly dose-dependent, with -41% on 0.7 mg, -53% on 1.35 mg, and between 66%-68% for the higher doses of 2 and 3 mg. However, this indicates that dose-dependent effects could only be seen up to doses of 2 mg, while for higher doses a plateau effect appeared to occur. The following table shows the main results:

Table 18: Summary of Percent Change from Baseline in Total Lymphocyte Counts by Treatment Group (Study APD334 002)

Treatment	Placebo	Etrasimod 0.7 mg	Etrasimod 1.35 mg	Etrasimod 2.0 mg	Etrasimod 0.35, 2.0 mg	Etrasimod 0.5, 3.0 mg
% Change from Baseline Lymphocyte Counts (Day 1)						
Mean (SE)	5.38 (3.93)	3.81 (7.58)	−16.75 (6.56)	−37.03 (4.97)	3.98 (5.08)	−5.01 (7.05)
% Change from Baseline Lymphocyte Counts (Day 21)						
Mean (SE)	5.08 (4.24)	−41.03 (3.19)	−53.43 (4.74)	−68.81 (2.60)	−67.34 (2.13)	−66.16 (3.40)
% Change from Baseline Lymphocyte Counts (Day 28, Follow-up)						
Mean (SE)	6.56 (6.28)	2.38 (5.85)	19.32 (12.77)	−4.75 (7.82)	−0.85 (6.08)	−0.92 (6.56)

Study APD334-109, designed as an "ethnic bridging study" used doses of 1 and 2 mg in Japanese and Caucasian healthy volunteers administered for 7 days. For both ethnic groups, the % reduction of peripheral lymphocyte counts was around 30% for the 1 mg groups, and 54% in the 2 mg groups. Differences between Japanese and Caucasian subjects were not detected. The primary pharmacology was therefore concluded to be independent from ethnicity/race.

Study ES101001 was a single- and multiple dose PK-PD study in Chinese healthy subjects which were dosed for a maximum of 14 days with doses of 1 mg, 2 mg, and 2 mg with a dose increase to 3 mg. Lymphocyte %reductions were seen at -41% for the 1 mg dose, -61% for the 2 mg dose, and -70% for the 3 mg dose. Whether the difference between the 2 mg and the 2/3 mg dose group represents a real dose-dependency remains, however somewhat unclear, since the duration of treatment was different in the two groups. The overall course of the lymphocyte count reductions are shown in the following figure:



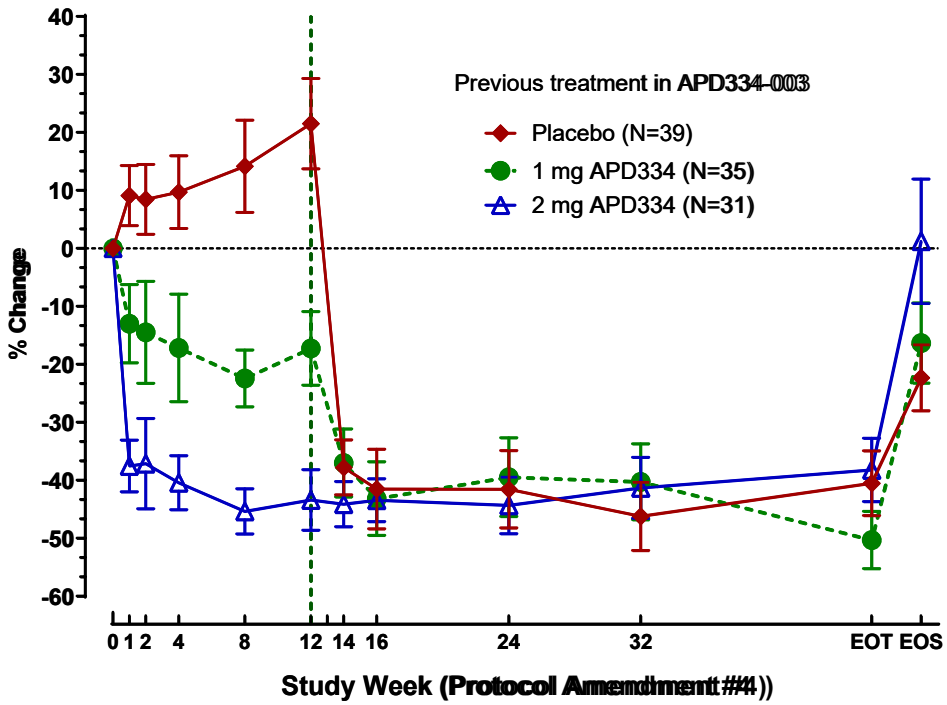
Data source: Table 14.5.1.1, Listing 16.2.8.2.1.
Note: Pharmacodynamic parameters were measured/derived based on the tests reported from the Covance Central Lab Service Panel.

Figure 9: Mean percent change from baseline of absolute peripheral blood lymphocyte count – pharmacodynamics set, study 1001001

Further data were collected in further 7 phase I studies (APD-008, -107, -108, -110, -111, -112, -115). The results confirmed those of the more dedicated studies, however, showed some variability, depending on the doses used, and the duration of treatment applied.

Lymphocyte count reductions have also been evaluated in patients within the phase 2 and phase 3 studies.

In the phase 2 study APC334-003, which investigated doses of 1 and 2 mg, the lymphocyte counts were evaluated at weeks 1, 8, and 12. The reductions observed were around 20% for the 1 mg dose, and 40% for the 2 mg dose, indicating a slightly lower relative effect as compared to what was observed in the 4 dedicated studies APD334-001, APD334-002, APD334-109, and ES100101. In the open-label extension study to this phase 2 study, the reductions were 40.5%, 50.3%, and 38.2% in the placebo, etrasimod 1 mg, and etrasimod 2 mg prior treatment groups at the end of treatment compared to baseline. The trial also showed a clear further reduction in those previously treated with 1 mg, and a similar reduction as observed for the active treatment groups, when patients were switched from placebo to the 2 mg dose (used as open-label treatment). The main results of this extension trial are displayed in the following figure:



Note: Weeks were defined from start of Study APD334-003. Only results from those subjects receiving etrasimod 2 mg at Study Week 12 and thereafter in Study APD334-005 are shown in this figure. Values represent mean (standard error of the mean).
Source: Study APD334-005 CSR Figure 17

Figure 10: Lymphocyte Counts (GI/L) Over Time by Treatment in Studies APD334 003 and APD334 005 (Modified Intent To Treat Evaluable Cohort; Study APD334 005)

In the phase 3 study APD334-301, the mean % reduction of lymphocytes increased from a -46% at week 2, to -55% at week 12 to 60% at week 52. Similar reductions were seen in study AOPD334-302 (which had a 12 week duration) which showed a -47% reduction at week 12, and a -60% reduction at week 12 (compared to placebo).

Overall, the effects on lymphocyte reduction in peripheral blood have been extensively studied with overall conclusive results, demonstrating reductions of up to almost 70% in healthy volunteers and up to 55% in patients. The reductions of peripheral lymphocytes occurred rapidly and was at least partially dose-dependent with some saturation of the effect above a daily dose of 2 mg. Of note, the phase 3 studies also partly evaluated the return to normal range, which was usually achieved within 2 weeks after discontinuation. A cross study comparison of the results is shown in the following table:

Table 19: Summary of Lymphocyte Response (PCFB) to Etrasimod (1–2 mg Once Daily) at Steady-State in Caucasian, Japanese, and Chinese Healthy and UC Subjects

a. Study	b. Ethnicity	c. Study Phase	d. Subjects	e. Daily Dose f. (mg)	g. Sampling Time (pre or postdose)	h. Time to Lymphocyte Nadir i. Mean (SD) j. (Days)	k. Lymphocytes %Change from Baseline l. Mean (SD)	m. Return to Normal Range (Days)
n. APD334-002	o. Caucasian	p. 1	q. Healthy	r. 2	s. 4 – 8 Hours Postdose	t. 11.5 (7.2)	u. −68.8 (8.2)[a]	v. 7[b]
w. APD334-109	x. Caucasian	y. 1	z. Healthy	aa. 1 bb. 2	cc. Predose dd. Predose	ee. 3.9 (1.7)	gg. −30.8 (17.6)	ii. NA

a. Study	b. Ethnicity	c. Study Phase	d. Subjects	e. Daily Dose f. (mg)	g. Sampling Time (pre or postdose)	h. Time to Lymphocyte Nadir i. Mean (SD) j. (Days)	k. Lymphocytes %Change from Baseline l. Mean (SD)	m. Return to Normal Range (Days)
						ff. 5.8 (0.93)	hh. −54.1 (7.5)	
jj. APD334-109	kk. Japanese	ll. 1	mm. Healthy	nn. 1 oo. 2	pp. Predose qq. Predose	rr. 5.29 (2.0) ss. 4.7 (1.6)	tt. −36.1 (11.8) uu. −53.6 (8.7)	vv. NA
ww. ES100101	xx. Chinese	yy. 1	zz. Healthy	aaa. 1 bbb. 2	ccc. 4 Hours Postdose ddd. 4 Hours Postdose	eee. 6.5 (2.8) fff. 7.4 (2.5)	ggg. −45.7 (9.1) hhh. −65.9 (8.0)	iii. NA jjj. 2
kkk. APD334-003	lll. Global	mmm.	nnn. UC	ooo. 1 ppp. 2	qqq. Predose rrr. Predose	sss. Not available	ttt. −24.3 (44.6) uuu. −43.2 (23.5)	vvv. 14[c]
www. APD334-301	xxx. Global	yyy. 3	zzz. UC	aaaa.	bbbb. Predose	cccc. 14[d]	dddd. −46.7 (23.5) WK2 eeee. −56.9 (20.9) WK52	ffff. 14[e]
gggg. APD334-302	hhhh. Global	iiii. 3	jjjj. UC	kkkk.	llll. Predose	mmmm. 14[d]	nnnn. −47.5 (23.6) WK2 oooo. −53.1 (20.8) WK12	pppp. 14[f]

[a] Mean percentage from baseline is by timepoint. Standard deviation determined mainly by the equation: standard error (SE) × square root number of subjects
[b] Time to return to within normal range
[c] Return to normal range was based on first follow up visit, 2 weeks after dose cessation
[d] 2 weeks (14 days) was first visit after initiation of etrasimod treatment
[e] 82% of subjects returned to normal range on first follow up visit, 2 weeks after dose cessation
[f] 77% of subjects returned to normal range on first follow up visit, 2 weeks after dose cessation
Lymphocyte value in normal range x10^9/L: APD334-002 [0.7 – 4.5]; APD334-109 [0.8 -4.8]
W2, Week 2; W12, Week 12; W52, Week 52
Source: Study APD334-002 CSR Table 14.3.12.7, Table 14.3.16.1.1 and Table 14.3.34.2, Study APD334-109 CSR Table 14.2.4.3, Study ES100101 CSR Table 14.5.1.1, Study APD334-003 CSR Table 14.2.19.3, Study APD334-301 CSR Table 14.2.32.3 and Study APD334-302 CSR Table 14.2.28.3

The results of the single studies were consistent with the PK/PD modelling analysis. This model was also used to simulate steady state lymphocyte responses to etrasimod and lymphopenia in 16-17 year-old adolescents.

Table 20: Summary of simulated steady-state lymphocyte responses for etrasimod 2 mg once daily in adults (age ≥ 18 years) and older adolescent (age 16 to < 18 years) patients with ulcerative colitis.

	Absolute Lymphocyte Count (10^9/L)	Lymphocyte Change From Baseline (10^9/L)	Lymphocyte Change From Baseline (%)
Age ≥ 18 years	0.797 (0.370, 1.65)	−0.778 (−1.84, −0.249)	−48.6 (−74.7, −21.3)
Age 16 to < 18 years	0.733 (0.336, 1.56)	−0.987 (−2.11, −0.397)	−58.5 (−77.8, −30.3)

Median (95% prediction interval)
Source code: sim-adolescent.Rmd
Source file: sim-adolescent-lc-ss.tex

Table 21: Summary of simulated steady-state percentages of subjects with absolute lymphocyte count below thresholds for etrasimod 2 mg once daily in adults (age ≥ 18 years) and older adolescent (age 16 to < 18 years) patients with ulcerative colitis.

	ALC < 0.2×10^9/L (%)	ALC < 0.5×10^9/L (%)
Age ≥ 18 years	0.100 (0.00, 0.300)	13.8 (11.8, 15.8)
Age 16 to < 18 years	0.200 (0.00, 0.600)	21.0 (18.6, 23.4)

Median (95% prediction interval)
ALC: absolute lymphocyte count
Source code: sim-adolescent.Rmd
Source file: sim-adolescent-lc-inc-ss.tex

The applicant has also investigated the effects of etrasimod on peripheral blood immune cell subsets were assessed in four Phase 1 studies in healthy volunteers (APD334-001, APD334-002, APD334-109 and ES101001) and two Phase 3 studies in subjects with UC (Studies APD334-301 and APD334-302).

All studies used flow cytometry to assess the immune subsets, however antibody panels and sampling differed between studies and in two studies (301 and 302), an epigenetic cell counting method was used. In study APD334-109 immunophenotyping was performed by 17-color flow on frozen PBMCs collected pre-dose, while the other phase 1 studies utilised versions of the clinical TBNK 8-color flow panel on fresh whole blood collected post-dose in Phase 1 studies and pre-dose in the Phase 3 studies. Results of the studies are therefore not always comparable.

The results of these investigations can be summarised as follows: Etrasimod induces a rapid, dose-dependent, partial and reversible reduction in in the frequency of peripheral total T cells (CD4 T cells including Th2 and Th17, CD8 T cells, naïve T cells, and central memory T cells) and B cells (CD19+ B cells and CD4+ and CD8+ cells). Peripheral blood CD19+ B cells and CD4+ and CD8+ cells were reduced with minimal impact on NK cells and monocytes. The reduction of T-helper cells (CD4+) was greater than the reduction in cytotoxic T cells (CD8+). Based on the missing influence on NK-cells an monocytes, the applicant claims that this important part of immune surveillance is not influenced by the compound. As an example, to show more detailed results, the following figure is displayed from the "ethnic bridging study" APD334-109:

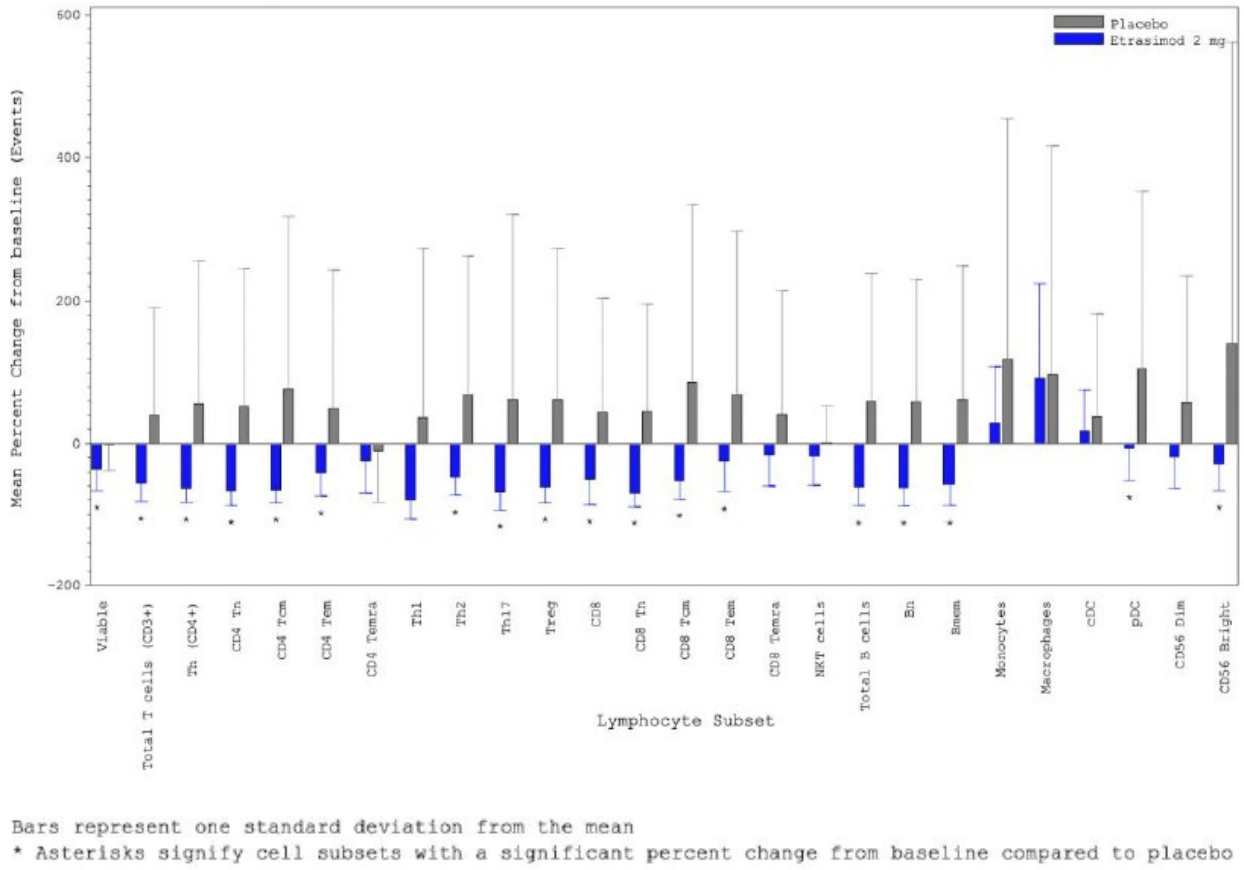


Figure 11: Summary of Day 7 Mean Percent Change from Baseline (Events) of 2 mg Etrasimod and Placebo (Mean of Japanese and Caucasian) – Study APD334-109

Even more detailed investigations were included in the phase 3 studies. In study APD-301 in which a subset of 283 patients was analysed (98 for placebo and 185 for etrasimod) subjects treated with etrasimod demonstrated nearly maximal reduction in CD3, CD4, CD8 and CD19 lymphocytes by Week 2, which was generally maintained through Week 52. Subjects treated with etrasimod achieved a significantly greater %change from baseline in these immune subsets at Week 12 and Week 52 compared to placebo. The overall greater effects on CD4 T cells and B cells as compared to CD8 T cells, and the minimal impact on NK cells and monocytes was confirmed. In study APD334-302, 188 patients (68 treated with placebo, and 120 treated with etrasimod 2 mg) were included in the biomarker analysis, the results of study 301 were generally confirmed without changes in absolute counts of monocytes and NK cells, creating a relevant increase in the relative abundance of these cells.

The applicant has therefore appropriately investigated the influence of the compound on peripheral immune cell subsets, demonstrating that the effects are mainly affecting CD4 T cells and B cells, while the counts of NK-cells and monocytes are generally not affected.

The applicant has also evaluated the influence of etrasimod on a wide variety of inflammatory proteins in the phase 2 and phase 3 studies, based on the evaluation of tissue from the biopsies. 10 of the most impacted proteins have been analysed in more detailed manner and showed results consistent with the effects on lymphocytes, with reductions in the vast majority of these proteins (e.g. CCL28, AL17A, MMP-1). In addition, it was shown that etrasimod reduced colonic CXCR3+ (Th1 and activated T cells) and Tregs in subjects with UC who achieved clinical and histologic remission. Th17 T cells and B cells were also reduced in subjects with UC who achieved clinical and histologic remission.

<u>Effects on heart rate:</u>

Initial binding of S1PR modulators to S1PR1 and S1PR3 on cardiac myocytes activates G protein-coupled inwardly rectifying potassium channels, which leads to potassium efflux, resulting in hyperpolarisation, reduced cell membrane excitability, and subsequent transient slowing in cardiac conduction prior to receptor internalisation and desensitisation. Transient bradycardia was therefore an expected effect during the development of etrasimod.

Across etrasimod clinical studies, HR effects were measured by three modalities: Vital signs (pulse rate), safety 12-lead ECG, and by continuous 12-lead ECG Holter/telemetry.

With respect to heart rate changes, the applicant has conducted two dedicated studies (Studies APD334-008 and -110), one of which also served as tQT study, and one of which was investigating different titration regimens in order to potentially mitigate the effects on heart rate. However, results with regard to heart rate reduction are included in all phase I studies.

The SAD study APD334-001 which used doses from 0.1 to 5 mg was demonstrating heart rate reductions at the 4-hour time-point which were dose dependant and showed the highest reductions in the doses of 3 mg to 5 mg, with mean reductions of -17 to -21 bpm.

A more granular evaluation was included in the MAD study APD334-002, which showed that HR nadirs were observed around 8 hours and 20 hours, the latter of which obviously related to the natural circadian rhythm of heart rate, which is slowest during sleep. The reductions of minimum heart rate overall showed a mean change from baseline between 5-6 bpm for placebo and the doses below 2 mg, and of 7-10 bpm for the doses of 2 mg and above. Generally, there was no HR decrease below 45 bpm, and the vast majority of subjects had a HR minimum between 55 and 60 bpm. This trial also observed a clear attenuation of the effects on the days following the first dose.

The overall results of this study (for days -1 to day 1) are shown in the following figure:

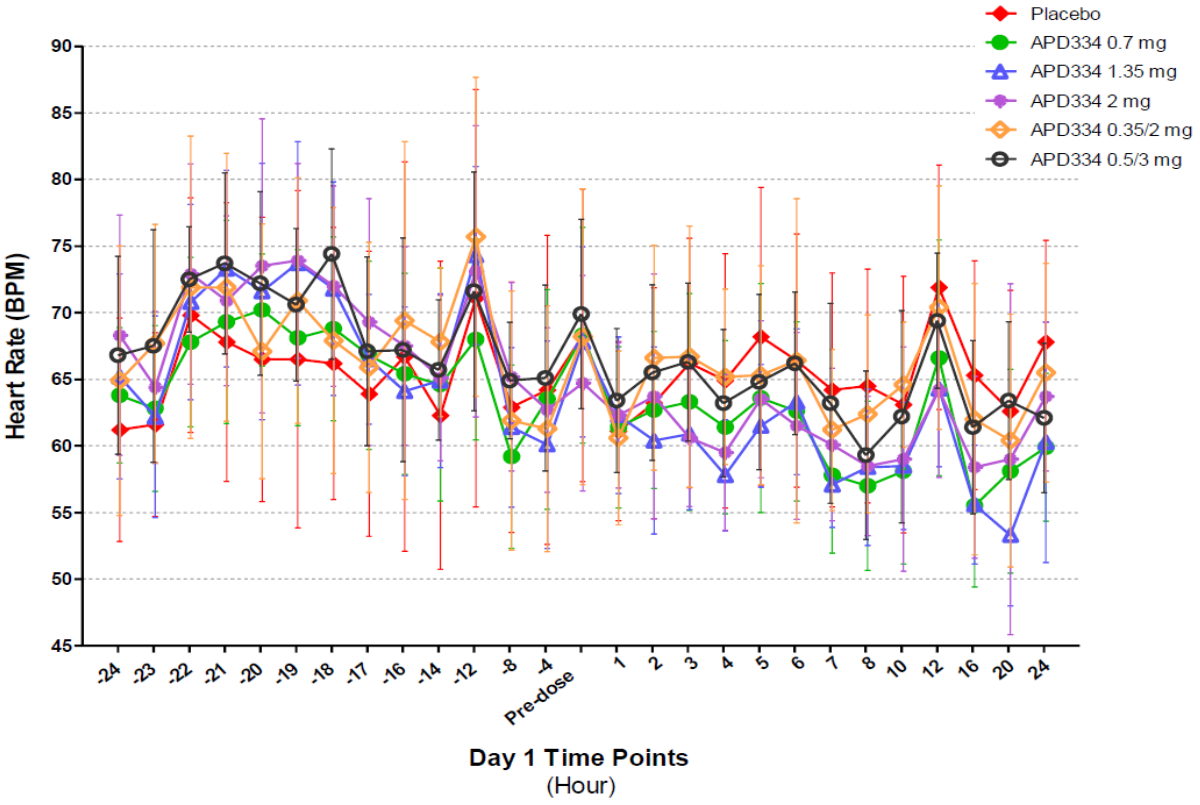


Figure 12: Mean Telemetry-Derived Heart Rate (bpm ± SD) by Dose Group by Hour: Day -1 through Day 1; Study APD334-002

The course of the effects for the days 1-3 is shown in the following figure:

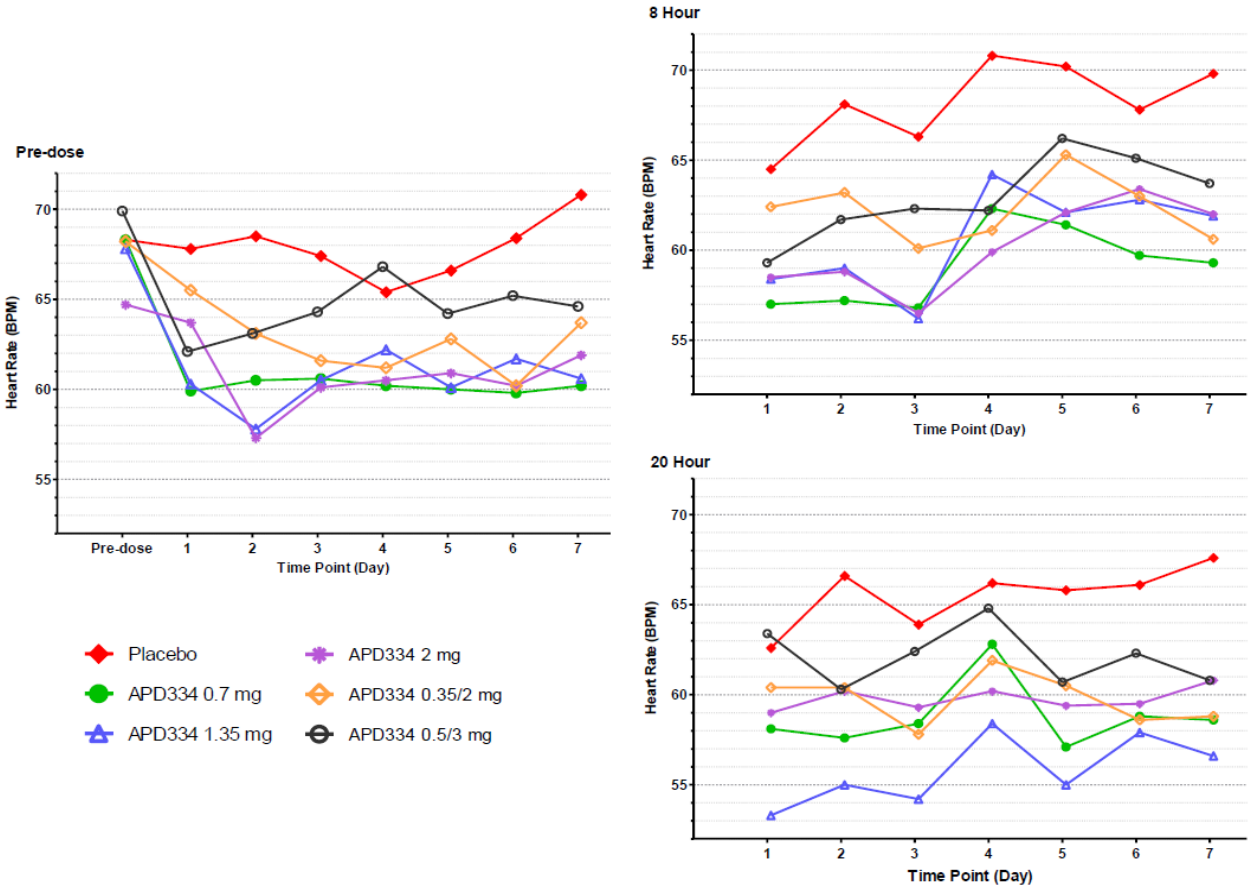
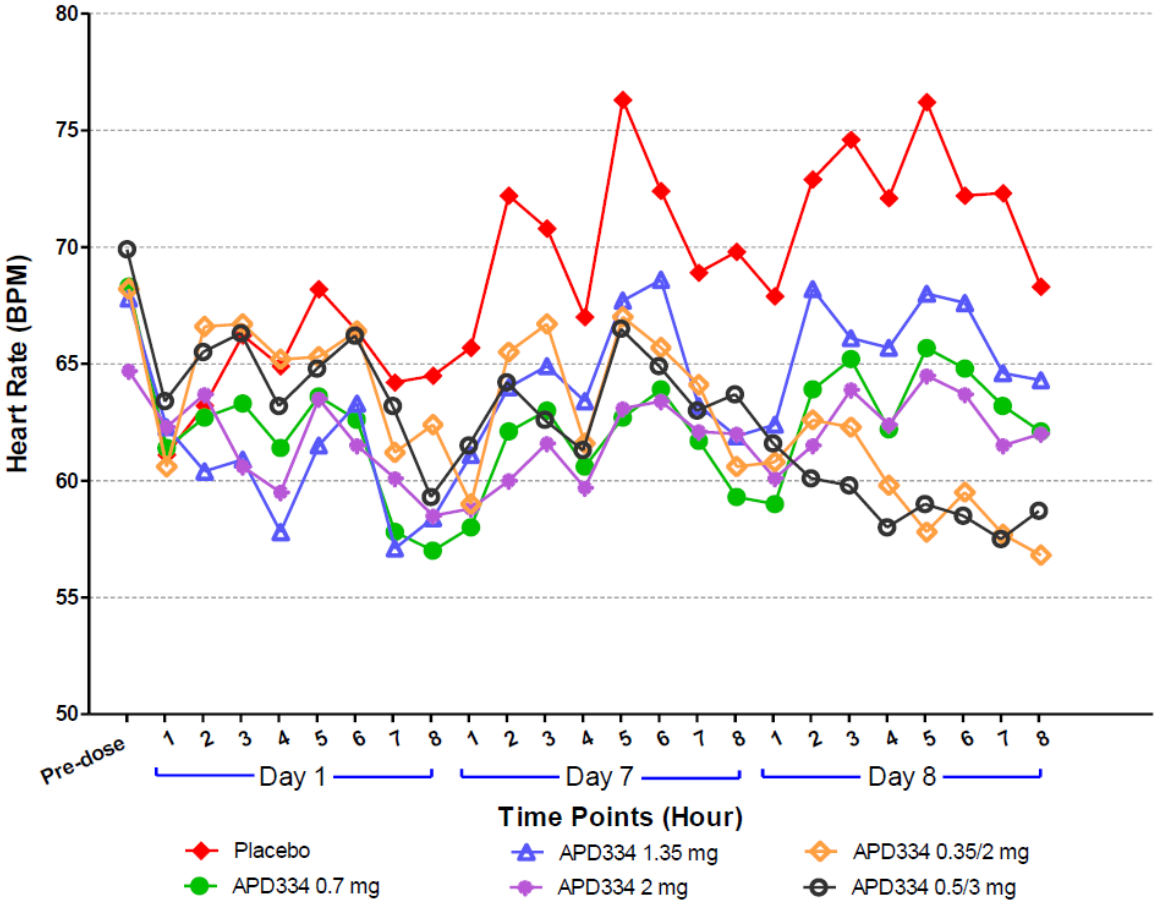


Figure 13: Telemetry-Derived Heart Rate (bpm): Pre-dose, Hour 8 (waking nadir) and Hour 20 (sleeping nadir) Day 1 through Day 8 (Mean)

This study also included two dosing groups with initial low doses of 0.35 mg and 0.5 mg which were increased to 2 mg and 3 mg respectively after day 7. This increase of the dose caused HR reductions that were similar in magnitude to the effects observed on day 1 for the rest of the doses administered (0.7 mg, 1.35 mg, and 2 mg). The data of the further course of the study also showed further reductions of the effects over time with no differences between doses. The results of this study indicate that using initial lower doses could not fulfil the purpose of mitigating the HR-reduction effects. This is shown in the following figure:



Source: Table 14.3.8.1

Figure 14: Mean Telemetry-Derived Heart Rate (bpm) by Dose Group: Days 1, 7 and 8 through 8 Hours Post-dose (Study APD334-002)

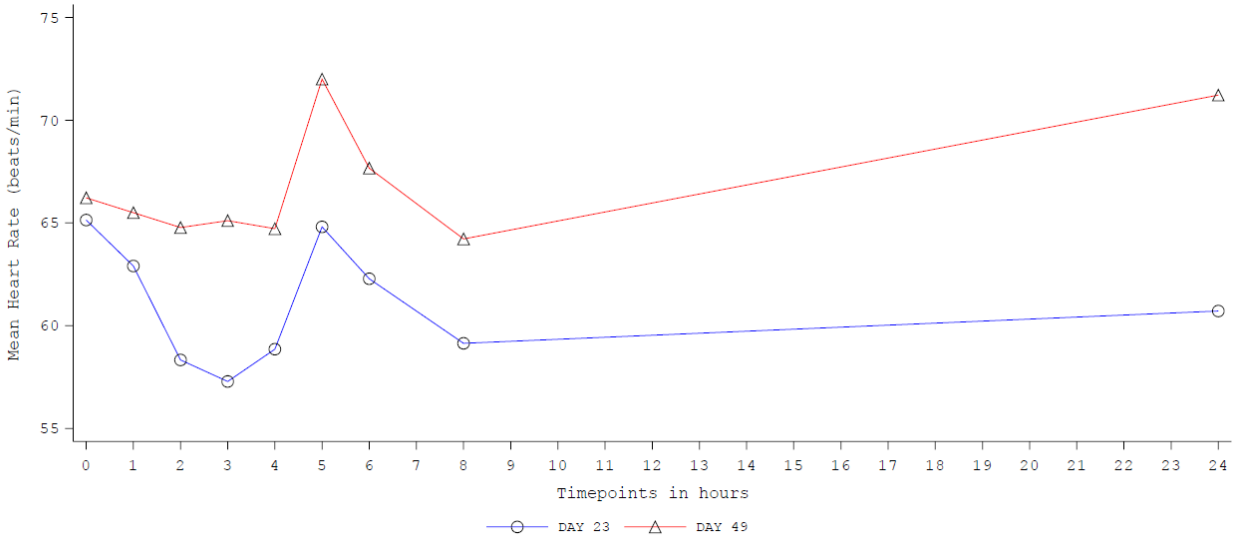
Study APD334-007, which was a relative bioavailability (of two different formulations) and food-effect study demonstrated that the effects on HR were more pronounced once etrasimod is taken without food. The maximum change occurred on day 1 in all dose groups, however while for both pharmaceutical forms used the mean HR reduction was around 13-15 bpm, this effect was at a mean of 8 bpm when administered in the fed condition. However, a similar study conducted with the commercial tablet (study APD334-114) did partly confirm this attenuating effect of food, although the magnitude of effect was slightly lower. In consequence of these results, the posology is that the compound should be taken with food for the first three days.

Study APD334-008, which was the tQT study, showed the largest change in heart rate at 3 hours postdose on day 1 with changes of more than 10 bpm between 2 and 6 and at 8 hours (highest reduction was -15.1 bpm at 3 hours). HR changes decrease on day 7, day 12 and day 14 with mean values of 8.5 bpm, 6.9 bpm, and 6.0 bpm. Relevant differences between the doses used (2 mg and 4 mg) were not detected.

Results of the previous studies were confirmed with the phase I studies APD334-009, -107, -108, -109, 111, -112, -115, 116, and ES101001. In these studies, the increase in plasma levels due to DDI, or due to liver impairment did not lead to a clear increase of the HR-reduction effects, and no differences between Japanese and Caucasian subjects were seen. Effects in Chinese subjects were generally considered similar to other racial/ethnic communities, although not direct comparison is available. The studies partly also demonstrate the vast attenuation of the effects with longer term

treatment, which is especially obvious in study APD334-111, which was investigating the interaction with oral contraceptives, and had a treatment duration of 49 days. The mean HR reduction after this treatment period was a mean of 2 bpm only.

The main results of this study are given in the following figure, making the first-dose and steady state difference most obvious:



Source: Figure 14.3.5.5.

Figure 15: Mean Heart Rate Over Time on Day 23 (First Dose Etrasimod; Etrasimod Alone) and Day 49 (Steady-State Etrasimod; Etrasimod + OC) (24-hour Electrocardiogram; Safety Set); Study APD334-111

Study APD334-110 was a dedicated cardiodynamic effects study, which investigated the potential for attenuating the HR reduction effects when etrasimod was administered with several titration regimens using both a "rapid desensitisation" (with small doses administered during the first 2 days and increase to 2 mg in day 3; 3 cohorts) or a "slow desensitisation" (with smaller, increasing doses used in the initial 6 days of treatment; 1 cohort). 95 subjects were studied in 5 different dosing cohorts (1 "control" with an immediate 2 mg dose).

The immediate intake of the full 2 mg dose on day 1 results in a clear difference in the HR decrease during the first 10-12 hours with this cohort being clearly more affected than any other treatment group. However, the HR reduction effect during sleep did not differ between the control cohort, and the rest of the "rapid desensitisation" cohorts. The cohort with the slow desensitisation, however, did not show a relevant HR decrease. A similar picture was observed on day 2. On day 3, however, the HR reductions were similar between the "control" cohort, and all the rapid desensitisation cohorts, with the overall magnitude of the effects in all cohorts (including the control cohort) not being relevantly different from day 1. The "slow desensitisation cohort", however, showed a similar HR reduction as the control cohort on day 1, or the "rapid desensitisation cohorts" on day 3, in day 6 when the full dose of 2 mg was administered for the first time.

The applicant therefore concludes that any titration regimen would lead to a delay in the occurrence of the heart rate lowering effects, rather than to an avoidance. Upon request, the applicant has presented a joint presentation of the data of the studies 202 and 110 demonstrating that the HR decrease more or less clearly depends on the final dose and the plasma concentrations, independent of the speed of, or doses during, a titration regimen. This is supported by the theoretical reflections on tolerance development, as well as the initially already presented PK/PD model.

HR reduction was also investigated in the phase 2 study APD334-003 which confirmed the dose-dependent effect, when comparing the 1 mg and the 2 mg doses. During this study, however, long-term observations clearly showed that the mean overall HR reduction on day 1, which was almost 10 bpm gradually decreased over time, and was observed as -4.3 bpm on day 8, -1.2 bpm on day 15, and even turned "positive" with a mean HR change of 1.4 bpm after 85 days.

The graphical presentation of the day 1 results are given in the following:

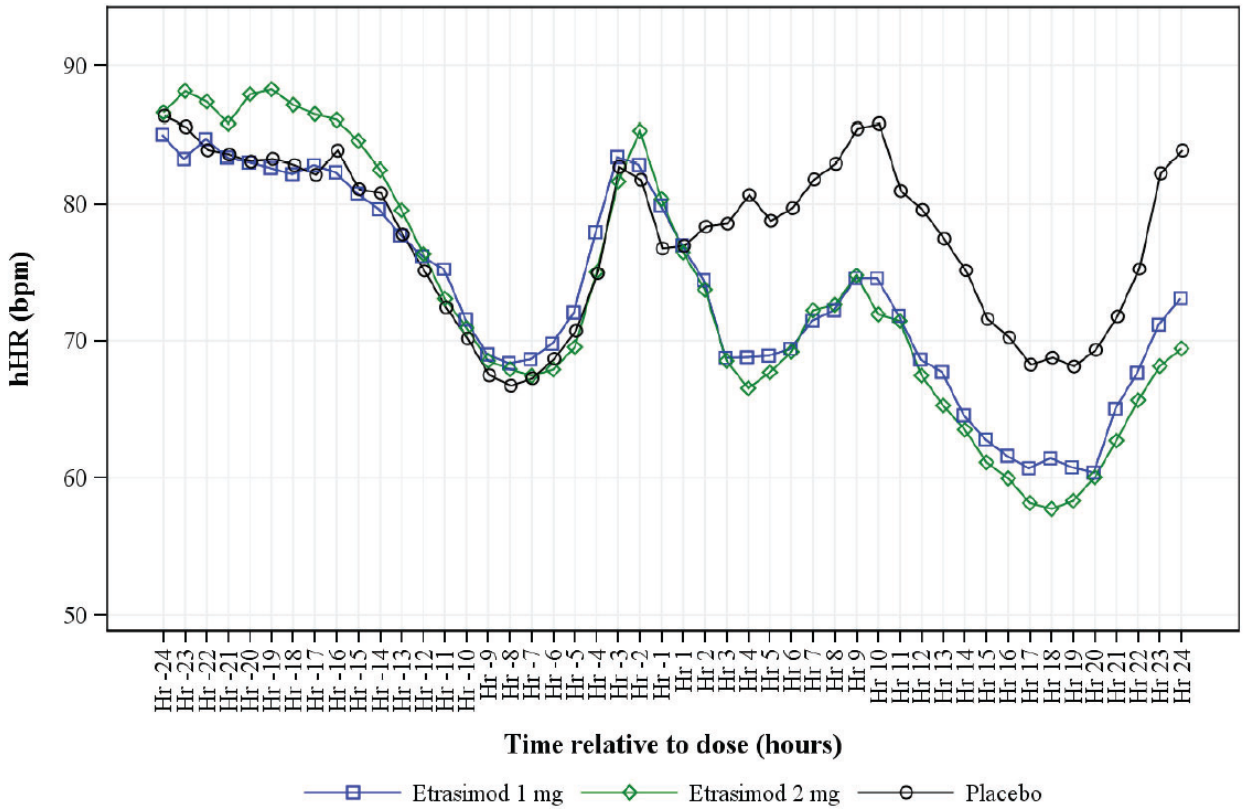


Figure 16: Mean hourly HR (hHR) by hour - Study APD334- 003 (HR set) Day 1

In the open-label extension study (study APD334-005), it was shown that the observed heart rate reduction compared to baseline was dependent on pre-treatment, with the previous placebo-treated patients experiencing a mean 8.8 bpm reduction on day 1, while the reduction was 3.3 for the etrasimod 1 mg prior treatment group, and 1.9 bpm for those continuing on 2 mg. The results are given in the following table:

Table 22: Summary of Safety ECG Heart Rate Maximal Observed by Timepoint Change from Baseline Over First 6 Hours Postdose by Prior Treatment Group on Day 1 (Study APD334 005)

	Etrasimod 2 mg (APD334-005)		
Heart Rate (bpm)	**Placebo Prior Treatment (APD334-003) (N = 42)**	**Etrasimod 1 mg Prior Treatment (APD334-003) (N = 38)**	**Etrasimod 2 mg Prior Treatment (APD334-003) (N = 32)**
Baseline[a]			
HR mean (SD) [Median (min, max)]	70.0 (12.5) [68.0 (53, 113)]	70.2 (11.4) [68.8 (54, 99)]	69.5 (10.4) [68.5 (51, 102)]
Day 1			
Observed Time of Maximal Change Postdose (hours)	3	2	4
HR Mean (SD) [Median (min, max)]	61.4 (10.0) [61.0 (40, 90)]	67.0 (10.6) [63.0 (49, 89)]	67.5 (9.7) [65.5 (53, 92)]
ΔHR Mean (SD) [Median (min, max)]	−8.8 (10.0) [−7.3 (−38, 11)]	−3.6 (6.6) [−3.0 (−23, 10)]	−1.9 (7.1) [−2.2 (−14, 20)]

[a] Baseline was the average of the ECG triplicate measurements taken at the Day 1 predose timepoint in Study APD334-005.
Source: Study APD334-005 CSR Table 14.3.3.10.1

During the phase 3 trial APD334-301, based on vital signs, the by timepoint largest mean reduction Change from Baseline HR was −7.3 bpm at 3-hour postdose and −0.4 bpm at 4-hour postdose for etrasimod and placebo groups respectively, with corresponding absolute mean HR of 66.7 and 75.5 bpm, respectively

In the phase 3 trial APD334-302, the largest mean reduction Change from predose Baseline HR was −7.3 bpm at 2 hour post-dose and −0.1 bpm at 1 hour post-dose for etrasimod and placebo, respectively; corresponding absolute HR mean was 67.0 bpm and 75.0 bpm, respectively.

Results from the phase 3 trials are displayed in the following two tables:

Table 23: Summary of Heart Rate Maximal Observed by Timepoint Change from Baseline on Day 1, from Vitals and Safety ECG (Study APD334 301)

Heart Rate (bpm)	**Vitals**		**Safety ECGu**	
	Placebo	**Etrasimod 2 mg**	**Placebo**	**Etrasimod 2 mg**
Baseline[a]				
n	144	289	139	272
HR mean (SD) [Median (min, max)]	75.8 (11.0) [74.0 (50, 108)]	73.9 (11.0) [72.0(50, 108)]	72.0 (12.03) [71.0 (50, 108)]	71.67(12.54) [70.0 (47, 126)]
Observed time of maximal change postdose (hour)	4	3	4	4
n	144	286	138	271
HR mean (SD) [Median (min, max)]	75.5 (10.2) [75.0 (52, 99)]	66.7 (10.5) [66.0 (42, 103)]	72.0 (11.07) [71.0 (46, 101)]	63.1 (9.37)) [62.0 (42, 99)]

Heart Rate (bpm)	Vitals		Safety ECGu	
	Placebo	Etrasimod 2 mg	Placebo	Etrasimod 2 mg
n	144	286	137	271
ΔHR mean (SD) [Median (min, max)]	−0.4 (7.7) [0.0 (−24, 18)]	−7.3 (8.8) [−6.5 (−50, 12)]	0.0 (8.55) [1.0 (−31,22)]	−8.6 (9.27) [−8.0 (−55, 15)]

Table 24: Summary of Heart Rate Maximal Observed by Timepoint Change from Baseline on Day 1, from Vitals and Safety ECG (Study APD334 302)

Heart Rate (bpm)	Vitals		Safety ECG	
	Placebo	Etrasimod 2 mg	Placebo	Etrasimod 2 mg
Baseline[a]				
n	116	238	115	235
HR mean (SD)	75.1 (9.21)	74.3(10.72)	70.3 (10.35)	71.0 (10.21)
[Median (min, max)]	[75.0 (56, 102)]	72.5 (52, 115)]	[70.0 (48, 101)]	[69.0 (49, 99)]
Observed time of maximal change postdose (hour)	1	2	4	4
n	116	238	114	233
HR mean (SD)	75.0 (10.44)	67.0 (10.04)	71.4 (11.09)	63.0 (9.38)
[Median (min, max)]	[74.0 (56, 112)]	[65.0 (46, 100)]	[70.0 (54, 110)]	[62.0 (44, 92)]
n	116	238	114	233
ΔHR mean (SD)	−0.1 (6.60)	−7.3 (9.69)	1.2 (8.5)	−7.9 (8.11)
[Median (min, max)]	[0.0 (−19, 18)]	[−6.0 (−38, 22)]	[1.0 (−21, 37)]	[−8.0 (−31, 15)]

Secondary pharmacology:

Study APD334-008 was a Phase 1, randomised, double-blind, placebo- and positive-controlled, parallel, ascending dose study to investigate the effect of multiple-doses of etrasimod (tablet formulations; 1 and 2 mg dose strengths) on the QT/QTc interval in 60 fasted healthy subjects. Due to the known heart rate effects, the supratherapeutic dose was introduced only after having received multiple doses of the standard dose of 2 mg. ECG, including Holter investigations were therefore done on days -1, 1, 7, 12, 14 and 15). Moxifloxacin was used as positive control. The use of the parallel design, which is also related to the HR reducing effects is therefore considered adequate.

The primary endpoint in this study was to be based on the ΔQTc with the selected primary correction method. This method selection was to be based on the observed HR reductions, which is considered acceptable. The correction method that resulted in the average on-treatment slope closest to zero (the smallest average SSS, as described by Tornøe et al) for each of the different QT/RR correction methods) for etrasimod and placebo was to be selected as the most appropriate HR correction method and was therefore to be used as the primary endpoint.

The largest heart rate effect (HR) exceeded 10 bpm on Day 1 only, but at none of the time points on higher doses. The correction coefficient for QTcI (mean ± SD: 0.31 ± 0.05) was similar to that of Fridericia (0.33), whereas the coefficient for QTcS was somewhat larger: 0.36 ± 0.05. When correction methods were tested for their ability to remove heart rate dependence, the SSS was consistently smaller for QTcS and larger for QTcP as compared to SSS for QTcF. On the other hand, scatterplots of QTc methods versus RR interval, showed that the slopes of the regression lines are closest to 0 for

QTcF (0.00015233 msec/msec) and QTcS (-0.00830 msec/msec). Based on this, results are detailed for both QTcF and QTcS (results for QTcI and QTcP also shown in graphical form).

There was a small effect of APD334 on change-from-baseline QTcF (ΔQTcF), without clear dose dependency. Mean ΔQTcF on placebo was mostly negative for the first 7 hours post-dosing, with somewhat more negative values on Day 14 (last 4 mg dose) than on Day 1 (2 mg, first dose), Day 7 (2 mg, last dose), and Day 12 (3 mg, last dose). On Day 14 (4 mg, last dose), mean ΔQTcF on placebo varied between -5.0 msec and -3.1 msec between the pre-dose and the 5 hours post-dose time point. On treatment with etrasimod, the largest ΔQTcF was seen at 10 hours on all dose levels with mean values of 2.7, 4.3, 3.7, and 3.8 msec on 2 mg first dose, 2 mg last dose, 3 mg last dose, and 4 mg last dose, respectively. With the exception of Day 1, an earlier peak effect was also seen around 2 hours post-dose on all doses, with mean values of 3.8, 3.0, and 3.3 msec on Days 7, 12, and 14, respectively.

The effects on QTcF are displayed in the following figure:

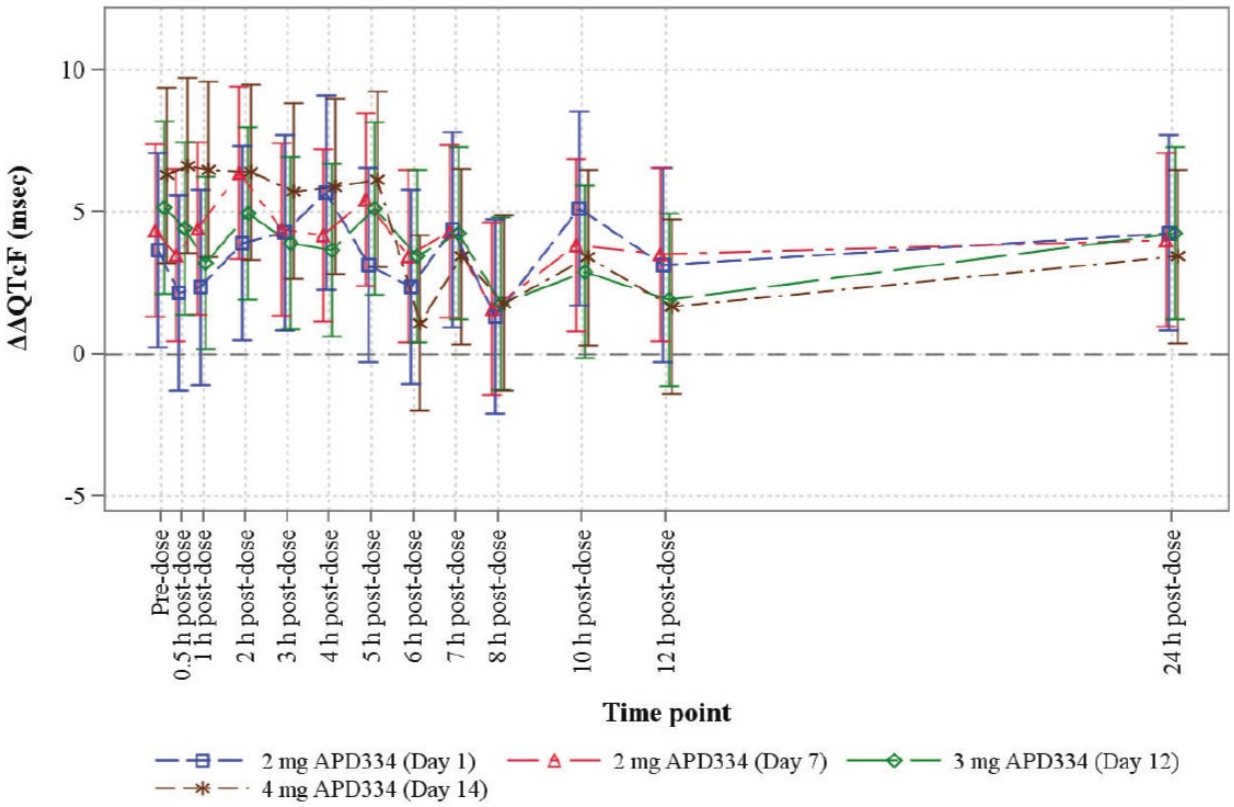


Figure 17: Placebo-corrected change-from-baseline QTc (ΔΔQTcF) across time points (QT/QTc analysis set); Study APD-008

Clear prolongation of QTcF was seen after dosing of 400 mg moxifloxacin, with the largest mean ΔQTcF of 15.7 msec at 4 hour post-dose, and mean ΔQTcF of 12.8 and 14.1 msec at 2 and 3 hours post-dose, respectively. Therefore, the study is considered to have sufficient assay sensitivity.

The effect of APD334 on ΔQTcS and on ΔΔQTcS was very similar to the effect on QTcF. The largest mean ΔΔQTcS on Day 1 (2 mg, first dose) was 4.0 msec at 4 hours post-dose, on Day 7 (2 mg, last dose) 4.9 msec at 2 hours, on Day 12 (3 mg, last dose) 4.5 msec at 0.5 hours, and on Day 14 (4 mg, last dose) 6.2 msec (90% CI: 2.98 to 9.44) at 1 hour post-dose. Results are also shown in graphical form below.

As with ΔΔQTcF, all upper bounds of the 90% CI across all days and time points post-dose were below 10 msec.

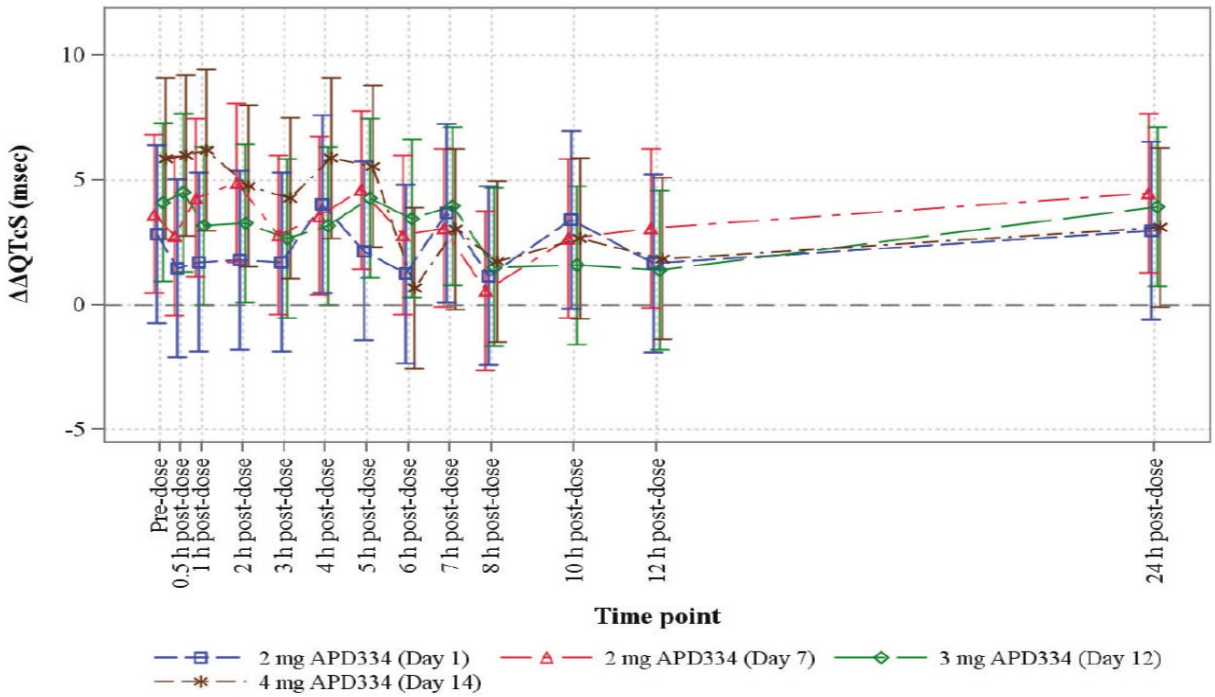


Figure 18: Placebo-corrected change-from-baseline QTcS (ΔΔQTcS) across time points (QT/QTc analysis set)

The categorical evaluations on QTcF or QTcS > 480 msec or ΔQTcF or ΔQTcS > 60 msecs were negative.

The applicant has also conducted an analysis/model of the course of the ΔΔQTcF against the plasma concentrations. The estimated slope of the APD334 concentration-QTc relationship was shallow and not statistically significant: 0.005 msec per ng/mL (90% CI: -0.0120 to 0.0229) with a moderately large, statistically significant intercept of 3.5 msec. The QT effect (ΔΔQTcF) with this model can be predicted to 4.13 msec (90% CI: 1.70 to 6.56), and 4.32 msec (90% CI: 1.47 to 7.18) at the observed geometric mean peak APD334 plasma concentrations for the 3 mg (122 ng/mL), and 4 mg (157 ng/mL) doses, respectively. Based on this analysis, a QT effect (ΔΔQTcF) exceeding 10 msec can be excluded within the observed range of APD334 plasma concentrations, up to ~270 ng/mL.

The resulting scatterplot evaluation is given in the following:

The relationship between the individual observed APD334 concentrations and ΔΔQTcF is shown in the following figure:

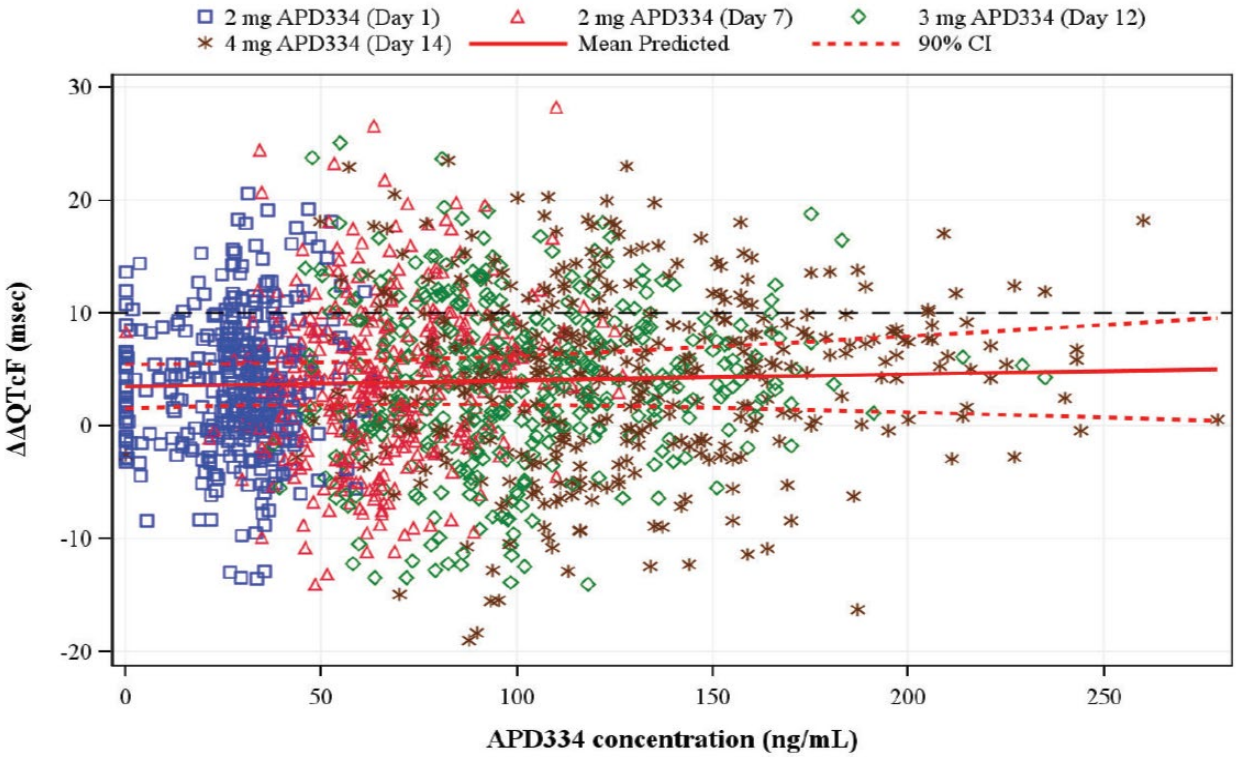


Figure 19: Scatterplot over pairs of observed APD334 plasma concentrations and estimated ΔΔQTcF by subject

Based on these analyses, it is concluded that etrasimod does not cause clinically concerning QTc prolongation.

PD interactions:

No studies on the potential of interaction with regard to immunosuppressive effects or on HR lowering or QT prolonging effects with substances with a similar PD action have been conducted. The applicant addresses the potential of add-on or potentiation of effects with those substances with warnings included in the PI. With regard to immunosuppressive therapies, this warning excludes corticosteroids, which were administered concomitantly in the phase 2 and phase 3 studies. This is acceptable.

With regard to HR reduction, the applicant presents a post-hoc analysis of the 28 patients from the phase 2/3 studies which have received a beta-blocker concomitantly when etrasimod was added to a stable bet blocker treatment, and for which no relevant difference for these effects were seen as compared to the rest of the population (-6.5 bpm vs. 7.2 bpm). While no significant difference is observed in reduction of HR, it needs to be taken into account that patients already on beta blockers had a lower baseline HR, also translating to lower HR following co-administration. Appropriate warning statements with regard to compounds also potentially having a negative chronotropic effect are included in the PI.

2.6.3. Discussion on clinical pharmacology

PK was evaluated over an extensive number of 15 Phase 1 studies in healthy subjects and special populations, as well as based on sparse sampling only in patients with UC in 2 Phase 2 and the 2 phase 3 studies. The Phase 1 studies involved PK assessments from a total of 641 healthy volunteer subjects, which included 22 subjects with hepatic impairment and 8 subjects with renal impairment. The Phase 2 and 3 studies involved PK assessments from 629 UC subjects treated with etrasimod (314 UC subjects received placebo). Furthermore, population PK modelling was applied.

Verification of data was in part difficult and very time-consuming, due to discrepant reporting between study reports vs. PK or other sub-reports /addenda, also affecting calculated values. There are still some concerns regarding reporting, e.g. determination of fraction unbound in ARE-R9986, long-term stability of analyte in matrix, and calculations for evaluation of the need for *in vivo* DDI studies based on *in vitro* results. However, these will not be further pursued due to the expected minimal influence on the overall benefit-risk conclusion.

To support etrasimod clinical studies, seven bioanalytical methods involving LC-MS/MS were developed and validated or qualified in accordance with the respective validation protocols and SOPs in effect. This included four validated methods for quantifying etrasimod or its M3 and M6 metabolites in K2-EDTA human plasma, one validated method for quantifying etrasimod in urine, one qualified etrasimod protein binding assay in human plasma, and one qualified chiral assay to separate and quantify etrasimod from its opposite enantiomer (AR401967). In addition to the above, two bioanalytical methods for moxifloxacin and the two components of a monophasic oral contraceptive (ethinyl estradiol/levonorgestrel) were developed and validated.

Validations involved precision, accuracy, selectivity and matrix effects, interference and specificity, dilution linearity, stability and carry-over. Validations generally followed the principles outlined in the EMA Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**), with deviations noted regarding long term stability in matrix regarding inclusion of adequate LTS QCs , matrix effect in special populations and regarding the qualification of the determination of the unbound fraction of etrasimod in plasma. However, these deficiencies were mainly considered minor in the context of the overall benefit risk assessment. Method transfer from Celerion to Covance laboratory was substantiated in a cross-validation showing acceptable ISR results.

In the bioanalysis of study samples, calibration standards and QC samples demonstrated adequate precision and accuracy and ISR met acceptance criteria regarding both the number of samples selected and the results achieved.

Food did not significantly affect the PK exposure of etrasimod 2 mg. However, food effects studies indicate somewhat attenuated HR reduction when etrasimod is administered with high-fat meal and hence it is recommended in the SmPC that etrasimod be administered with food for the first 3 days to attenuate potential transient heart rate lowering effects related to initiation of treatment. Etrasimod can then be taken with or without food.

ADME properties of etrasimod have been properly characterised.

Hydroxyl metabolite M3 (AR503641) and ketone metabolite M6 (AR504344) as minor metabolites not requiring further investigation has proven unacceptable. Originally, both metabolites were identified as major metabolites in the metabolic profiling of AUC0-168h individual subjects plasma pools in the human mass balance study APD334-107, but were later classified as minor metabolites by the applicant based on a subsequently generated AUC0-312h cross-subject pool. The latter had been initiated in deviation from the protocol because the original AUC0-168h pools were found to represent only ~75% of the total radioactivity (mean AUC0-infinity) due to avoidable deficiencies in the study protocol. Although more temporally comprehensive individual subject AUC pools would have been more appropriate from the outset, the integrity of the AUC0-312h cross-subject pool (representing ~90% of the mean AUC0-inf for total radioactivity) was found insufficient for metabolite profiling and identification. Contributing plasma samples were exposed to significantly different storage conditions and increased storage time, which may have biased the outcome in terms of metabolites identified and their proportion of circulating total drug related radioactive material. Furthermore, neither the study protocol, the bioanalytical study plans nor the study and various bioanalytical reports did provide enough (pre-) specification to sufficiently ensure reliability of the presented results by excluding the possibility that the analyses were adjusted during performance in favour of desired results. Furthermore, the human mass balance study APD334-107 failed to meet the criteria in

CPMP/EWP/560/95/Rev. 1 Corr. 2** for extrapolation to steady state.

Given that the metabolite classification based on AUC0-312h from study APD334-107 can neither be regarded reliable nor representative for steady state, the findings from two non-radioactive multiple dose studies (APD334-008 and APD334-002) indicating that M3 and M6 are major metabolites at steady state must be considered.

In addition, in study APD334-109, the metabolite-to-parent ratio for AUC24 on Day 7 at steady-state was >30% for both M3 and M6, which warrants further investigation of DDI potential of metabolites, according to the ICH M12 guideline (AUCmetabolite ≥ 25% of AUCparent and also account for at least 10% of drug-related material in circulation), even though *in vitro*, compared to etrasimod, M3 and M6 are 10-fold and 3-fold less potent at S1P1, respectively, and 91-fold and 1.5-fold less potent to S1P5 receptor, respectively.

Both metabolites exhibit higher accumulation ratios of up to ~5 in healthy adult Caucasian subjects (study APD334-109) as compared to <3 observed for etrasimod across multiple dose studies, consistent with the longer half-lives of the metabolites. What is more, disproportionally increased exposures of M3 and M6 (based on AUC) were observed in subjects with mild, moderate and severe hepatic impairment (study APD334-108) and following co-administration with itraconazole (ADP334-116) and are similarly expected in subjects with low body weight below 40 kg.

Overall, the recommendation was therefore made to investigate the metabolites M3 and M6 *in vitro* as both perpetrators and victims of potential DDIs, and to address their effect on QT prolongation by an automated patch-clamp test on M3 and M6 for their effects on the hERG potassium channel current *in vitro* (non-GLP) as post-authorisation measures. The applicant has agreed to the post-licensing profiling of the *in vitro* enzyme (CYP inhibition, CYP induction, UGT inhibition) and transporter (gut, hepatic, renal) DDI for both M3 and M6 as "perpetrator", to the *in vitro* enzyme phenotyping (CYP and UGT) and transporter (substrate of P-gp, BCRP, OATP1B1/B3) DDI for both M3 and M6 as "victim", as well as to the submission of an in-vitro hERG study. To that effect, the applicant has provided a corresponding letter of commitment.

Effect of renal impairment on PK of etrasimod was investigated in dedicated study APD334-112. The renal impaired subject group did not comply with guideline recommendations, being a mixed group of 2 severe renal impaired subjects and 6 subjects with ESRD requiring dialysis, and in these etrasimod was administered following dialysis, which likely removes uremic toxins. This is not ideal, since worst-case scenario should be able to evaluate possible impact of accumulation of uremic toxins (lower eGFR but still not requiring dialysis) on hepatic elimination pathways. Nevertheless, etrasimod exposure overlapped in subjects with severe renal impairment and ESRD and was comparable to the exposure in matched participants with normal renal function. Therefore, the applicant's proposal that no dose adjustment is necessary for patients with mild, moderate, or severe renal impairment is considered acceptable.

The PK of the metabolites M3 and M6 was however significantly, and disproportionally changed and metabolic ratio was reduced in severe renal impairment. Elucidation of the metabolite portfolio and relative frequencies in severe renal impairment was originally planned in study APD334-112 as exploratory objective but was then not conducted. Therefore, the characterisation of M3 and M6 as substrates, inhibitors and inducers of key enzymes and transporters is recommended to the applicant as a post-authorisation measure in order to provide information regarding their risk for drug interaction and to contribute to a better understanding of metabolism and elimination of etrasimod, M3 and M6. The result will also be relevant in the treatment of frail populations such as patient with severe renal impairment.

Effect of hepatic impairment on PK of etrasimod was investigated in the dedicated study APD334-108. In severe hepatic impairment, geometric mean AUCinf was ~1.6-fold higher in severe hepatic impairment than in matched participants with normal hepatic function, with the upper bound of 90%CI suggesting that increase could be up to 2-fold, which would be outside the therapeutic window. Etrasimod 2 mg is hence contraindicated in patients with UC and severe hepatic impairment. No dosing restriction is necessary in patients with mild and moderate hepatic impairment.
The fraction unbound showed an unexpected trend for decrease which was attributed to low subject numbers and variability, questioning its overall meaningfulness in the study.

Elimination of metabolites appeared to be impacted by reduced liver function. Exposures of metabolites M3 and M6 were found significantly increased in a disproportional manner as compared to etrasimod in mild, moderate and severe hepatic impairment. MR was increased accordingly for both M3 and M6, and mean t1/2 generally prolonged. As stated above, further *in vitro* investigation of M3 and M6 is considered warranted regarding potential for interaction at key enzymes and transporters, as well as with regard to QT prolongation and has been recommended to the applicant. The applicant has agreed to conduct a post-authorisation *in vitro* evaluation of the effects on hERG channel and of the potential for DDI at key enzymes and transporters as perpetrator and victim for both M3 and M6 (see above).

Weight was a significant covariate in population PK modelling. Model-predicted etrasimod exposure for subjects < 40 kg was 1.5-fold higher than exposure of typical 70 kg subject. While it is agreed that most adult patients are weighing >40 kg, the target population also includes patients ≥ 16 years in whom such low weights may occur more frequently. Since the argumentation relies mainly on modelling, observed data for lymphocyte counts and the events qualified as ADRs were submitted for the patients of the lowest weight group. No weight related trends regarding safety endpoints were observed. Body weight related exposure differences are described in the SmPC section 5.2. Based on Pop PK analysis, sex, race, ethnicity and age had a minimal impact on etrasimod exposure. It is agreed that no dose adjustment based on these covariates is necessary. No significant differences in etrasimod PK are expected between adults and older adolescent patients (age 16 to < 18 years) with UC, but very limited data is available for older adolescent patients.

CYP2C8, CYP2C9, and CYP3A4 were identified the main CYP enzymes involved in etrasimod metabolism from *in vitro* and *in vivo* studies.

Based on the increases in etrasimod observed in study APD334-009 upon coadministration with fluconazole, a moderate inhibitor of CYP2C9 and CYP3A4, and a strong inhibitor of CYP2C19, co-administration of etrasimod with a therapeutic agent or a combination of agents that are moderate to strong inhibitors of two or more of the following CYP enzymes (CYP2C8, CYP2C9, and CYP3A4) (e.g., fluconazole) is not recommended.

Coadministration of etrasimod with rifampin, a moderate inducer of CYP2C8 and CYP2C9 and a strong inducer of CYP2C19 and CYP3A4 in study APD334-009 decreased etrasimod total plasma exposure. As all the enzymes induced by rifampin contribute to the oxidative metabolism of etrasimod, co-administration of etrasimod with rifampin or any other inducers that affect multiple CYPs is not recommended and caution should be exercised.

Regarding co-administration of etrasimod with inhibitors of CYP enzymes, CYP2C9 poor metaboliser status present in <5% of the population also needs to be taken into account. The use of etrasimod is not recommended when co-administered in patients who are known or suspected to be CYP2C9 poor metabolisers (< 5% of the population) and who take medicinal products that are moderate or strong inhibitors of CYP2C8 and/or CYP3A4 due to the risk of increased exposure of etrasimod.

When etrasimod was coadministered with oral contraceptives containing EE/LVG, EE was increased by 24%, and this information is reflected in the PI, consistent with PI of other medicinal products causing increase in EE of similar magnitude, as risk for AE may be increased.

Etrasimod appears unlikely to produce a clinically meaningful inhibition or induction of key CYP enzymes, or inhibition of membrane transporters based on *in vitro* studies and evaluation whether a clinical DDI study was required.

Based on *in vitro* experiments, etrasimod does not seem to be a substrate of P-gp, BCRP, OATP1B1 and OATP1B3, OAT1, OAT3, OCT1, or OCT2 transporters.

No information about the potential for interaction has been presented for the two metabolites M3 and M6 so far. The applicant has agreed to profile for both M3 and M6 the potential for DDI at key enzymes and transporters as both perpetrator and victim *in vitro* as post-authorisation measure.

PD

The applicant has evaluated the critical PD properties of the compound relating to the "desired" immunosuppressive effects of the substance with investigating in very broad manner the reduction of counts of peripheral lymphocyte counts, which is regarded to form the basis of the efficacy observed in the phase 3 studies. Lymphocyte count reduction following etrasimod treatment initiation was rapid. In healthy volunteers receiving multiple dose etrasimod, time to lymphocyte nadir was ranging from 4 to 11 days, consistent with time to reach PK steady-state. In Phase 3 pivotal studies with UC patients, time to lymphocyte nadir was 14 days. However, this was the first time point for evaluation after treatment initiation and it is presumably shorter. Mean lymphocyte count reduced to approximately 50% from baseline and was maintained during 52 weeks of treatment with etrasimod QD. Lymphocyte count reductions were reversible and returned to normal values in majority of UC patients within 2 weeks of dose discontinuation. Other investigations also included the analysis of the subpopulation of the lymphocyte reductions, and have also shown results as expected, in demonstrating that mainly CD4 T cells (and some other T-cell subpopulations) and B-cells were reduced, but that there was almost no influence on NK cells, and monocytes. However, whether this prevents the occurrence of immune-suppression mediated adverse events is a question that can be solved on safety data, as well as (potentially) post-licensing pharmacovigilance data, only. Adequate contraindications and warnings with regard to immunodeficiencies, and active infections are given. The lymphocyte reducing effects are also described extensively in the Chapter 4.4 of the SmPC, and advice is included for the interruption of treatment with lymphocyte counts below certain thresholds, and when experiencing serious infections. A statement on the potential for the occurrence of PML has also been included based on the similar mode of action with other compounds of the class. Caution is also given for concomitant immunosuppressive medication, including a statement that only corticosteroids have been included in the clinical studies as concomitantly administered immunosuppressive medication.

As expected, the compound possesses an initial HR lowering effect, which is most pronounced during the first 8 hours after administration, and during sleep on this first day of administration. The effect is attenuated over time and appears to be less pronounced in patients. The effects have been sufficiently characterised, both in healthy volunteers and in UC patients, including the investigation of potential attenuation of the initial effect with dose titration. The evaluations based on the phase 2 and phase 3 studies do show a somewhat decreased magnitude of the HR reduction effects in patients, as compared to healthy subjects that were documented in the phase 1 studies. However, the variability of changes is relatively high, and includes values of potential concern, up to 50 BPM reductions. It is repeatedly demonstrated that the HR reductions are attenuated over time, with long-term treatment showing mean reductions of HR usually under 5 bpm. However, again, variability is high, and includes changes up to or even above 20 bpm as compared to the observed baselines. For the documentation of the PD properties, the investigations performed, and the conclusions drawn appear to be adequate. Due to the effects on HR, certain patient groups, however, are excluded from treatment. Based on the data submitted, the conclusion that the proposed posology with a full 2 mg dose to be given from the first day, is adequate. Since only healthy volunteers, or patients without heart rate conduction problems have been included in the studies, there was no clear indication that the HR lowering would

lead to clinically significant adverse reactions (see safety evaluation). Nevertheless, the applicant has taken account of these effects with adequate warnings and contraindications in the PI (e.g. excluding patients with recent CV events, history of AV- and SA- block. The HR reduction effects are described in section 4.4 of the SmPC, and adequate warnings are included for the risks associated with patients having bradycardia or AV-block (or recent myocardial infarction or heart failure) at the start of treatment. Treating physicians are instructed to monitor patients hourly for four hours at the first day of administration, and to additional monitor patients up to 8 hours in case of warning signs (e.g. heart rate below 45 bpm, new onset AV block, increase of QTc above 500 msec). Cardiologist advice is requested before treating certain subgroups of patients, including those with a history of symptomatic bradycardia, including syncope, and with untreated sleep apnoea.

A dedicated DDI study has not been conducted with beta blockers or calcium channel blockers. The potential for interaction with heart rate lowering compounds has been included in the Chapter 4.5 of the SmPC, including the potential for inducing relevant QT prolongation in patients with bradycardia when using Class Ia and Class II anti-arrhythmics concomitantly.

The applicant has also adequately evaluated the potential for QT prolongation with an extensive tQT study. The study demonstrated that the potential for QT prolongation with the substance is low, and from this point of view the substance is devoid of concerning effects.

2.6.4. Conclusions on clinical pharmacology

The pharmacodynamics, including secondary pharmacodynamics have been extensively and sufficiently studied. The PK of etrasimod is considered overall acceptably characterised Furthermore the CHMP recommends and the applicant has agreed to profile the *in vitro* enzyme (CYP inhibition, CYP induction, UGT inhibition) and transporter (gut, hepatic, renal) DDI for both M3 and M6 as "perpetrator", and to the *in vitro* enzyme phenotyping (CYP and UGT) and transporter (substrate of P-gp, BCRP, OATP1B1/B3) DDI for both M3 and M6 as "victim". Furthermore, an effect on QT prolongation of M3 and M6 will be evaluated post authorisation by an automated patch-clamp test on M3 and M6 for their effects on the hERG potassium channel current *in vitro* (non-GLP).

2.6.5. Clinical efficacy

The studies submitted for the support of efficacy are presented in the introduction to clinical aspects above. 3 studies are considered relevant for the documentation of efficacy at this point of time.

2.6.5.1. Dose response studies

One dose-response study is presented in support of efficacy and, of dose-selection.

Study APD334-003:

This study was designed as a phase 2, proof of concept and dose-ranging, placebo-controlled multi-centre study comparing two doses of etrasimod (1 mg and 2 mg) with placebo for a treatment duration of 12 weeks. This study was conducted at 87 study sites in 17 different countries.

The main objectives of the trial were defined as follows:

1. Primary objective:

- To determine the effect of treatment with APD334 in inducing clinical remission at 12 weeks.

2. Secondary objectives:

- To determine the effect of treatment with APD334 in inducing clinical response at 12 Weeks
- To determine the effect of treatment with APD334 on endoscopic improvement at 12 weeks

The target population consisted of male or female subjects aged between 18 and 80 years (inclusive), with moderately to severely active UC (who have received a formal and documented diagnosis of ulcerative colitis at least 6 months prior to screening), defined as an adapted CMS of 4 to 9 that included an endoscopic subscore of ≥ 2 and a rectal bleeding score of ≥ 1. In addition, subjects were to have inadequately responded to, responded initially but then lost response, or were intolerant to 5-ASAs, corticosteroids, immunosuppressive agents, tumour necrosis factor alpha (TNFα) antagonists, and/or integrin antagonists over the 5-year period prior to study entry.

Subjects eligible for the double-blind treatment based on the study inclusion and exclusion criteria were randomly assigned to one of the following 3 treatments in a 1:1:1 ratio: etrasimod 1 mg, etrasimod 2 mg, or placebo.

Up to 240 subjects were planned to be randomised into the study, with the understanding that the Sponsor could end the study at any time. Randomisation was stratified by presence or absence of current oral corticosteroid usage and previous exposure to TNFα antagonists. The number of subjects with previous exposure to TNFα antagonists was capped at 50% (or at most 120 subjects with prior exposure to TNFα antagonists were to be randomised). The efficacy endpoints at Week 12 were analysed in the ITT population using the multiple imputation method to handle missing data. An SAP was drawn up before the end of the trial (dated 27 February 2018). Significance level was determined at 5% to be tested one-sided.

- The primary efficacy variable in this proof-of-concept study was change from baseline in "adapted Mayo Clinical Score (MCS)", which means the 3-component MCS (score ranging from 0 to 9, including stool frequency, rectal bleeding, and findings on endoscopy) at Week 12. Initially, this variable was labelled PMS #1. This variable was since renamed to "adapted MCS" to better reflect the predominant nomenclature.

The secondary endpoints were the following:

- Proportion of subjects who achieved endoscopic improvement at Week 12. Endoscopic improvement was defined as Mayo endoscopic subscore (using findings of flexible proctosigmoidoscopy) of ≤ 1 point.
- Improvement in 2-component MCS (score ranging from 0 to 6, including rectal bleeding and findings on endoscopy) at Week 12.
- Improvement in total Mayo Score (TMS) (score ranging from 0 to 12, including stool frequency, rectal bleeding, findings on endoscopy, and PGA) at Week 12.

Additional exploratory endpoints were also defined, including additional operational evaluations of the Mayo Scores, including subscores, measures of health-related Quality of Life and biomarkers.

For the trial, 303 patients were screened, and 147 were determined to be screen failures, whereas 156 patients were included with n=52/50/54 patients in the etrasimod 1 mg/etrasimod 2 mg and placebo treatment groups, respectively, of which 47, 46, and 48 completed the study.

Overall, demographic characteristics were similar across the 3 treatment groups. The mean (SD) age of subjects was 43.2 (12.22), 40.4 (12.39), and 44.8 (14.85) years in the etrasimod 1 mg, etrasimod 2 mg, and placebo groups, respectively.

Disease characteristics at baseline were generally similar across the 3 treatment groups and were representative of a population of subjects with moderately to severely active UC. The median duration of UC was 4.8 to 6 years across the treatment groups. The median adapted MCS was 7.0, the median

TMS was 9.0, the median IBDQ total score was 122.0, and the median CRP concentration was 4.6 mg/L.

The history of previous treatment showed that 25-36% of the patients used corticosteroids concurrently, 28-34% had a previous history of TNF-alpha use, and 33%-61% for "conventional" immunosuppressants, 8-22% to integrin antagonists, and 92-98% to 5-ASAs.

For the primary efficacy parameter, a mean change from baseline of −1.9, −2.5, and −1.5 points was seen at Week 12 in the adapted MCS for the etrasimod 1 mg, etrasimod 2 mg, and placebo groups, respectively.

Using the multiple imputation method to handle missing data, a statistically significant (p = 0.0091) change from baseline was demonstrated for the mean difference from placebo at Week 12 in the adapted MCS for the etrasimod 2 mg group (LS mean [SE] difference: −0.99 [0.42]) compared with the placebo group. There was an estimated −0.4 point mean change from baseline in the adapted MCS at Week 12 in the etrasimod 1 mg group relative to placebo, which was not statistically significant (p = 0.1457).

Using the MITT population – which restricted the population to those with baseline as well as week 12 data available, the following was achieved, as shown in the table:

Table 25: Change From Baseline in the Adapted MCS at Week 12, ANCOVA (MITT Population); Study APD334-003

				Between-group Comparison[a]		
Group	**n**	**LS Mean (SE)**	**90% CI**	**Difference in LS Means (SE)**	**90% CI**	**p-value**
Etrasimod 1 mg	49	−2.01 (0.32)	−2.54, −1.48	−0.50 (0.42)	−1.21, 0.20	0.119
Etrasimod 2 mg	44	−2.54 (0.33)	−3.08, −2.00	−1.04 (0.44)	−1.76, −0.31	0.010
Placebo	48	−1.51 (0.31)	−2.03, −0.98			
Etrasimod 2 mg vs 1 mg				−0.53 (0.44)	−1.25, 0.19	0.112
Linear contrast trend test						
Test statistic	5.6					
p-value	0.019					

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; LS, least squares; MITT, modified intent to treat; n, number of subjects in analysis; SE, standard error.

[a] Comparison with placebo, unless otherwise specified.

Note: The adapted MCS consists of 3 of the 4 subscores found in the complete MCS as follows: stool frequency, rectal bleeding, and findings of flexible proctosigmoidoscopy. Total score for the adapted MCS range: 0 to 9, each component ranging from 0 to 3 (0 = normal, 1 = mild, 2 = moderate, 3 = severe).

Statistical analysis was based on ANCOVA model with terms for treatment, current oral corticosteroid use, prior exposure to tumor necrosis factor alpha antagonists and baseline value as covariate. One-sided p-value was used from the model.

Linear contrast coefficients (for the trend test): −1 for placebo, 0 for etrasimod 1 mg, and 1 for etrasimod 2 mg.

Source: Table 14.2.2.3.1

The secondary endpoints gave the following results:

Table 26: Results of Secondary Efficacy Endpoints at Week 12 Using Multiple Imputation Method to Handle Missing Data- Study APD334-003

Secondary Efficacy Measures	**Etrasimod 1 mg (N=52)**	**Etrasimod 2 mg (N=50)**	**Placebo (N=54)**
Endoscopic improvement			
% of subjects with endoscopic improvement	22.5	41.8	17.8
MH estimate for difference in % (SE)	4.1 (7.98)	24.4 (8.87)	
90% CI for difference from placebo	−9.1, 17.2	9.8, 39.0	
1-sided p-value	0.3059	0.0030	
2-component Mayo Score			
LS mean (SE) change from baseline	−1.30 (0.22)	−1.75 (0.22)	−0.92 (0.21)
LS mean (SE) difference from placebo	−0.39 (0.28)	−0.84 (0.29)	
90% CI for LS mean difference from placebo	−0.85, 0.08	−1.32, −0.36	
1-sided p-value	0.0858	0.0020	
Total Mayo Score			
LS mean (SE) change from baseline	−2.69 (0.41)	−3.35 (0.41)	−2.08 (0.39)
LS mean (SE) difference from placebo	−0.60 (0.53)	−1.27 (0.55)	
90% CI for LS mean difference from placebo	−1.48, 0.27	−2.17, −0.37	
1-sided p-value	0.1277	0.0100	

Abbreviations: CI, confidence interval; LS, least squares; MH, Mantel-Haenszel; N, number of subjects; SE, standard error.

The difference from placebo for score measure was estimated using analysis of covariance and proportions measures was estimated using MH. Both methods were adjusted for current oral corticosteroid therapy at baseline and previous exposure to tumor necrosis factor alpha antagonists.

Source: Table 14.2.21.12, Table 14.2.21.3.2, and Table 14.2.21.4.2

The exploratory endpoints were in general in support of the primary and secondary endpoints. The rate of patients in clinical remission (3-component) was 8.1%, 16.0%, and 33.0% in the placebo, 1 mg, and 2 mg etrasimod groups, respectively. The proportions of patients with histological healing in these 3 groups was 10.2%, 20.4%, and 31.7%.

The study report presents a couple of sensitivity analyses (with different imputation methods for missing values etc), but this was restricted to the etrasimod 2 mg comparison to placebo. Generally, the sensitivity analyses were in line with the "primary" analyses.

Statistically significant results were achieved from the 2 mg etrasimod group only, whereas all other comparisons were without demonstration of statistical significance.

The study clearly demonstrated that the 2 mg dose was the only dose to be superior to placebo treatment. Since higher than 2 mg doses were considered to be burdened with potentially unacceptable cardiac toxicity (HR reduction), the 2 mg dose was finally selected for the phase 3. Although this study did not have a full confirmatory approach, the selection of the dose is considered acceptable.

2.6.5.2. Main studies

The applicant presented as pivotal evidence for efficacy, two randomised, placebo-controlled studies comparing the proposed 2 mg – dose with placebo. Since the design of the trials was identical for the first 12 weeks of treatment (and only the long-term period deviates in study APD334-301 from the study -302), the planning, and design of the studies is presented jointly, whereas results are displayed separately.

Studies APD334-301 and APD334-302

Methods

Both pivotal studies included identical 12-week double-blind induction treatment periods. Treatment in Study APD334-302 ended after the 12-week double-blind induction treatment period. However, Study APD334-301 was a treat-through study that included an additional 40 week double-blind treatment period after the 12-week induction for a total treatment duration of 52 weeks (etrasimod 2 mg or placebo).

For Study APD334 302, all subjects who completed the 12-week treatment had the option to enter the OLE study, provided the eligibility criteria were met. After Week 12 or at any time during the 40 week Double-Blind Maintenance Treatment Period of Study APD334 301, subjects had the option to enter the OLE study (APD334-303), if in the opinion of the Investigator the subject's UC had not improved or had worsened compared to Baseline (Week 0/Day 1) and provided other eligibility criteria were met

- **Study Participants**

Subjects were 16 to 80 years of age. The pre-treatment related criteria were defined as follows:

Demonstrated an inadequate response to, loss of response to, or intolerance to at least 1 of the following therapies:

- Conventional therapy:
  - Oral 5-ASA compounds (Note: Oral 5-ASA was not included in the list of conventional therapies in the region-specific protocol for VHP countries.)
  - Corticosteroids

        - Thiopurines
    - Biologic therapy or JAK inhibitor therapy
        - TNFα antibodies (eg, infliximab, adalimumab, golimumab or biosimilars)
        - Anti-integrin antibodies (eg, vedolizumab)
        - Anti-IL-12/23 antibodies (eg, ustekinumab)
        - JAK inhibitors (eg, tofacitinib)

The medication used to qualify a subject for entry into the study must have been approved in the country of conduct of the study, and an "adequate course" of therapy "according to local guideline" must have been administered.

Disease specific criteria were the following:

- Diagnosed with UC ≥ 3 months prior to screening confirmed by endoscopy and histology.
- Active UC confirmed by endoscopy with ≥ 10 cm rectal involvement. Subjects with proctitis only at Baseline who meet the other eligibility criteria for inclusion, including the endoscopic and RB criteria for moderate to severe disease, were capped at 15% of the total subjects enrolled.
- Moderately to severely active UC defined as MMS of 4 to 9, including an ES ≥ 2 and RB score ≥ 1.

Inadequate response and loss of response, and intolerance were defined as follows:

- Inadequate response: Signs and symptoms of persistently active disease despite a history of completing a dosing regimen.
- Loss of response: Recurrence of symptoms of active disease during treatment following prior clinical benefit.
- Intolerance: Including, but not limited to infusion- or injection-related reaction, demyelination, congestive heart failure, infection, or any other related AE that led to a reduction in dose or discontinuation of the medication.

The key exclusion criteria comprised the following items:

- Severe extensive colitis (e.g. with need for imminent hospitalisation and/or surgery; fulminant colitis, toxic megacolon, perforation) or history of these elements, partial or total colectomy.
- Hospitalisation for extensive colitis with need for i.v. corticosteroids.
- Diagnosis of CD or indeterminate colitis, or fistulae (consistent with CD).
- Diagnosis of microscopic, ischaemic, or infectious colitis.

Previous treatment with 3 or more biologics or with 2 or more biologics and a JAK inhibitor were also excluded.

During the study, subjects were permitted to take therapeutic doses of nonbiologic therapy for UC (oral 5-ASA, oral corticosteroids, or medicinal probiotics), provided the dose was stable prior to randomisation and during the treatment period.

- **Treatments**

Subjects in both studies were randomised in a 2:1 ratio to receive either etrasimod 2 mg or placebo once daily. Randomisation was stratified by: (a) naïve to biologic or JAK inhibitor therapy at study entry (yes or no); (b) Baseline corticosteroid use (yes or no); and (c) Baseline disease activity (MMS 4 to 6 or 7 to 9).

- **Objectives**

The primary objective of both studies was defined "to assess the efficacy of etrasimod when administered for 12 weeks on clinical remission in subjects with moderately to severely active UC", and the secondary objective as: "to assess the efficacy of etrasimod when administered for 12 weeks on clinical response, symptomatic response and remission, endoscopic changes, and mucosal healing in subjects with moderately to severely active UC".

The objectives of trial 301 were described in very similar manner as for study -302. The only difference was that throughout, the efficacy and safety was to be evaluated over 12 as well as over 52 weeks of treatment.

There was also a safety objective defined as "to assess the safety of etrasimod after daily doses of 2 mg for 12 weeks in subjects with moderately to severely active UC", and "other objectives" which included evaluation of etrasimod PK and the effect of etrasimod on health-related subject-reported outcomes and biomarkers.

The study design scheme for both studies is given in the following figure:

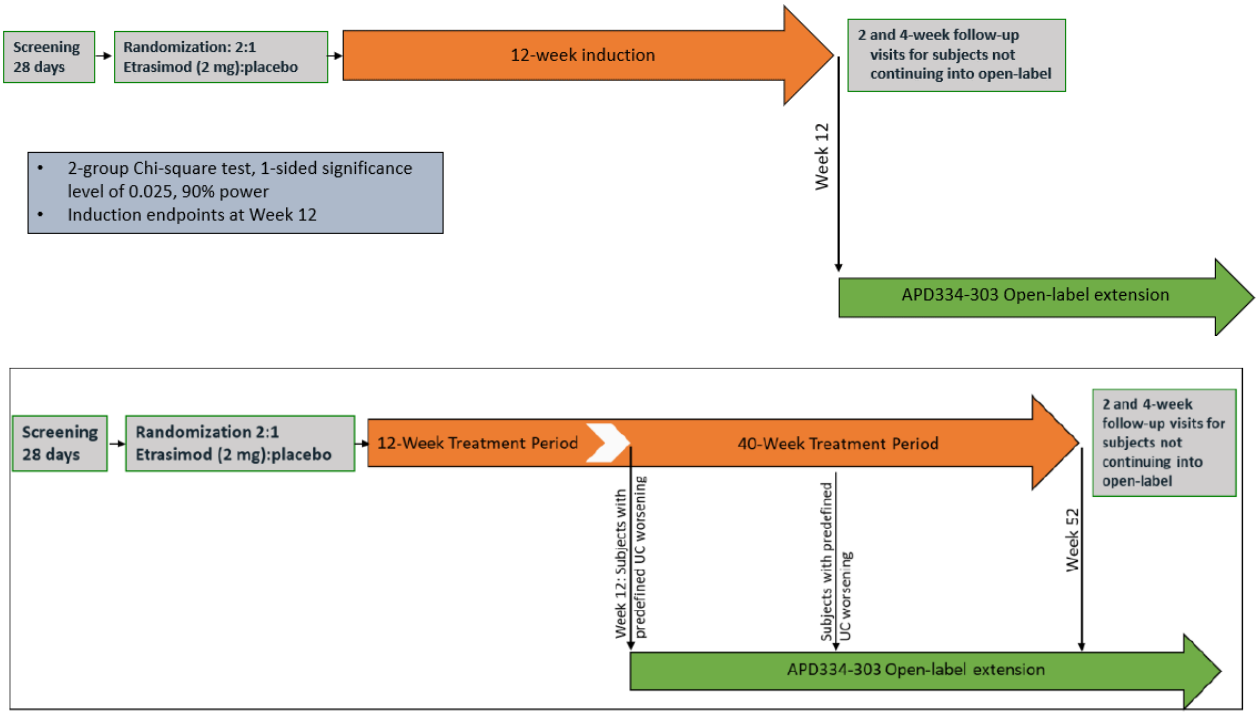


Figure 20: Overview on study design of studies APD334-301 and 302

Scheduled visits occurred at Week 0/Day 1 and at Weeks 2, 4, 8, 12 for both studies, and at 16, 20, 24, 32, 40, 48, and 52 weeks in study 301.

At the end of the 12-Week Induction Treatment Period in study 302, subjects had the option to enter an OLE Study APD334-303 provided they met eligibility criteria. Subjects who did not participate in the OLE study had 2-Week and 4-Week Follow-Up Visits after their last dose of study treatment.

Subjects in study 301 who experienced disease worsening following the completion of the Week 12 Visit, or who experienced disease worsening during the 40-Week Treatment Period, or who completed all study procedures at Week 52, had the option to enter OLE Study APD334-303 provided they met eligibility criteria. Subjects who did not participate in the OLE study had 2-Week and 4-Week Follow-Up Visits after their last dose of study treatment.

Subjects in study 301 who experienced disease worsening following the completion of the Week 12 Visit, or who experienced disease worsening during the 40-Week Treatment Period, or who completed all study procedures at Week 52, had the option to enter OLE Study APD334-303 provided they met eligibility criteria. Subjects who did not participate in the OLE study had 2-Week and 4-Week Follow-Up Visits after their last dose of study treatment. The rules defining disease worsening were initially referring to a "2-consecutive day" rule with criteria for the symptoms RB and SF. In the later course of the study, these criteria were changed to a "14 day" rule, which did not longer require the occurrence of the symptoms (with similar definition) on 2 consecutive days, but at 2 timepoints at least 7 but not more than 14 days apart. The intent of the change was to lower the rate of discontinuations, which have indeed decreased as shown by an additional analysis. However, no differential effect on the two treatment groups could be detected.

- **Outcomes/endpoints**

The primary efficacy endpoints evaluated etrasimod versus placebo in:

- The proportion of subjects achieving clinical remission at Week 12
- The proportion of subjects achieving clinical remission at Week 52 (study 301 only)
    - Clinical remission was based on the MMS and was defined as SF subscore = 0 (or = 1 with a ≥ 1-point decrease from Baseline), RB subscore = 0, and ES ≤ 1 (excluding friability and hereafter referred to as ES ≤ 1).

The "key" secondary endpoints were the following:

- The proportion of subjects achieving endoscopic improvement at Week 52 (study 301 only)
- The proportion of subjects achieving endoscopic improvement at Week 12
- The proportion of subjects achieving symptomatic remission at Week 52 (study 301 only)
- The proportion of subjects achieving symptomatic remission at Week 12
- The proportion of subjects, in clinical remission at Week 52 and who had not been receiving corticosteroids for ≥ 12 weeks prior to week 52 (study 301 only)
- The proportion of subjects with mucosal healing at Week 52 (study 301 only)
- The proportion of subjects with mucosal healing at Week 12
- The proportion of subjects achieving clinical remission at both Weeks 12 and 52 (study 301 only)

The applicant has assigned a couple of "other secondary endpoints" which were defined as follows:

- The proportion of subjects achieving clinical response at Week 12 (and 52 in study 301) with clinical response defined as a ≥ 2-point and ≥ 30% decrease from baseline in MMS, and a ≥ 1-point decrease from baseline in RB subscore or an absolute RB subscore ≤ 1.
- The proportion of subjects achieving endoscopic normalisation at Week 12 (and week 52 in study 301) defined as ES = 0

- The proportion of subjects achieving symptomatic remission at Weeks 2, 4, 8 and week 16, 20, 24, 32, 40, and 48 in study 301
- The proportion of subjects achieving complete symptomatic remission at each study visit (Weeks 2, 4, 8, 12; and 16, 20, 24, 32, 40, and 48 in study 301) with complete symptomatic remission defined as RB=0 and SF=0.
- The proportion of subjects achieving non-invasive clinical response at each study visit (Weeks 2, 4, 8, 12: 16, 20, 24, 43, 40, 48, and 52 in study 301) with non-invasive clinical response defined as ≥ 30% decrease from baseline in composite RB and SF, and a ≥ 1-point decrease from baseline in RB subscore or an absolute RB subscore ≤ 1
- The proportion of subjects achieving symptomatic response at each study visit (Weeks 2, 4, 8, 12; and week 16, 20, 24, 32, 40, and 48 in study 301)

A couple of these "other secondary" endpoints were only applicable to study 301, such as:

- The proportion of subjects who had not received corticosteroids for ≥ 4 weeks and achieved clinical remission at Week 52 among subjects receiving corticosteroids at baseline
- The proportion of subjects achieving clinical response at both Weeks 12 and 52
- The proportion of subjects with mucosal healing at both Weeks 12 and 52
- The proportion of subjects achieving endoscopic normalisation at both Weeks 12 and 52
- The proportion of subjects who had not received corticosteroids for ≥ 4 weeks and achieved clinical remission at Week 52 among subjects receiving corticosteroids at baseline

In addition to these, "exploratory efficacy endpoints" were defined as follows:

- The proportion of subjects with remission and response using total Mayo Clinic score at Week 12 (and week 52 in study 301) (with Clinical remission using TMS: Total Mayo Clinic Score of ≤ 2 points with no individual subscore of > 1 point and Clinical response using TMS: A ≥ 3-point and ≥ 30% decrease from baseline in Total Mayo Clinic score, and a ≥ 1-point decrease from baseline in RB subscore or an absolute RB subscore ≤ 1)
- The proportion of subjects with histologic improvement at Week 12 (and 52 in study 301) (as defined by the Geboes Index, Robarts Histopathology Index, and Nancy Histologic Index) with the definitions used as follows: Geboes Index score < 3.1 (not given for the other scores in the protocol, for actual use oc criteria, see results).
- The proportion of subjects with histologic remission at Week 12 (and week 52 in study 301) (as defined by the Geboes Index, Robarts Histopathology Index, and Nancy Histologic Index) with a Geboes Index score < 2.0 (not given for the other two scores; see below in the results).
- The proportion of subjects with improvement in extraintestinal manifestations (EIMs) at Week 12 (and week 52 in study 301) in subjects with EIMs at Baseline
- The proportion of subjects with endoscopic improvement and histologic improvement (defined as ES<=1 and Geboes ≤ 3.1) at Week 12
- The proportion of subjects with Geboes score of 0 at Week 12
- MMS and Change from Baseline by visit
- RB, SF, and composite RB/SF subscores and change from Baseline by visit
- The proportion of subjects with an RB = 0 by visit
- The proportion of subjects with a ≥ 1 point decrease from Baseline in RB by visit

For study 301 only, the following were defined as exploratory secondary endpoints:

- Time to loss of response, with loss of response defined by:
    - A ≥ 2-point increase from Week 12 in the combined SF + RB scores and combined SF + RB score of ≥ 4, on 2 consecutive visits (≥ 7 days apart) and confirmed by centrally read ES ≥ 2.

The following endpoints termed "additional endpoints" were also to be evaluated:

• Scores and change from baseline to Week 12 (and in addition at week 52 in study 301) in the following:

- IBDQ total score
- UC-PRO/SS
- SF-36, version 2, physical and mental component and domain scores
- WPAI-UC
- Urgency NRS
- Abdominal pain NRS
- The proportion of subjects with UC-related hospitalisations
- The proportion of subjects requiring UC-related surgeries, including colectomy

Study 302 also included the determination of etrasimod PK (in conjunction with the HR/ECG evaluations) on day 1, and weeks 2, 4, 8, 12, and (in case applicable) follow-up visits after 2 and 4 weeks.

Biomarker endpoints to be evaluated comprised the following in both studies: Faecal calprotectin, hs-CRP, and lymphocyte counts.

- Change from baseline in level of fecal calprotectin at Weeks 2, 4, 8, and 12

Pre-planned sub-group analyses were foreseen for the following categories: Sex, Age (cut-off 65 years), race, baseline oral corticosteroid use, region (North America, Western Europe, Eastern Europe, Other), extent of disease (proctosigmoiditis, left-sided colitis, pancolitis, proctitis), prior treatment with 5-ASA only, naïve to biologics and JAKs (yes/no; as well as number of prior biologic/JAK therapies and prior failure to these therapies), baseline disease activity according to MMS (4-6 or 7-9), baseline FC (cut-off: median), baseline CRP (cut-off: median), baseline TMS (cut-off: 8).

The applicant has also compiled an "Addendum - clinical study report" to study APD334-302 which analysed post-hoc the following endpoints:

- Ad hoc analysis of the proportion of subjects with both endoscopic normalisation (i.e., endoscopic score [ES] = 0) and histologic remission (i.e., Geboes Index score < 2.0) at Week 12.
- Ad hoc analysis of the proportion of subjects with absence of abdominal pain or urgency (i.e., a score of 0 on a 0 to 10 numeric rating scale [NRS]) at Week 12.
- Exploratory ad hoc analysis at Week 12 for the proportion of subjects who achieved clinical remission with rectal bleeding/stool frequency (RB/SF) subscores of the modified Mayo Score (MMS) using a modified calculation to average daily subscores from within a 7-day window with a minimum of 3 consecutive days of completed diary entries or 4 non-consecutive days.

- Analysis of primary (clinical remission), key secondary (endoscopic improvement, symptomatic remission, and mucosal healing) endpoints by predefined subgroups in the FAS with Baseline MMS 5 to 9 were conducted as part of the original SAP for this study; however these analyses were omitted from the CSR and therefore are presented in this addendum.
- Clinical response was assessed in the study as a secondary endpoint and the analysis by subgroup in the FAS population with MMS 5 to 9 at Week 12 is presented as an ad hoc analysis.

A similar clinical Study Report Addendum was provided for study 301 which evaluated in addition the following post-hoc defined endpoints:

- An ad hoc analysis of the proportion of subjects with both endoscopic normalisation (i.e., endoscopic score [ES] = 0) and histologic remission (i.e., Geboes Index score < 2.0) at Week 12 and Week 52.
- Ad hoc analysis of the proportion of subjects with absence of abdominal pain or urgency (i.e., a score of 0 on a 0 to 10 numeric rating scale [NRS]) at Week 12 and Week 52.
- An exploratory ad hoc analysis at Week 12 and Week 52 for the proportion of subjects who achieved clinical remission with rectal bleeding/stool frequency (RB/SF) subscores of the modified Mayo score (MMS) using a modified calculation to average daily subscores from within a 7-day window with a minimum of 3 consecutive days of completed diary entries or 4 non-consecutive days.
- Analysis of primary (clinical remission), key secondary (endoscopic improvement, symptomatic remission, corticosteroid-free clinical remission, mucosal healing and sustained clinical remission) endpoints by predefined subgroups in the FAS with Baseline MMS 5 to 9 were conducted as part of the original SAP for this study; however, these analyses were omitted from the CSR and therefore are presented in this addendum.
- Clinical response was assessed in the study as a secondary endpoint and the analysis by subgroup in the FAS population with MMS 5 to 9 at Week 12, Week 52, and at both Week 12 and Week 52 is presented as an ad hoc analysis.

It was noted that the planned endpoints did not account for the requested co-primary evaluation of endoscopic response/remission, and symptomatic remission as given in the CHMP UC guideline. Since the objectives of the trial were met, and the secondary endpoints outside the "key secondary" endpoints fully covered the EU-required criteria, a relevant concern cannot be raised, except for the fact that an endpoint "corticosteroid free symptomatic remission at 52 weeks" was not included, which was evaluated only post-hoc, but showed similar to the overwhelming majority of all secondary endpoints (see further below). At request, also other "corticosteroid free" success endpoints were evaluated and showed similar results.

Sample size

For study 302, based on a 2-group Fisher's exact test, a 1-sided significance level of 0.025, and a 2:1 randomisation ratio, 330 total subjects are required to achieve at least 90% power to detect a difference of 12.5% in the primary endpoint of clinical remission at Week 12 between the etrasimod treatment group 18.5% and the placebo treatment group 6.0%.

For study 301 the sample size estimation was based on a 2-group Fisher's exact test, a 1-sided significance level of 0.025, and a 2:1 randomisation ratio. This resulted in a number of 420 total subjects required to achieve 93.4% power in order to detect a difference of 13.5% in the primary endpoint of clinical remission at Week 52 between the etrasimod treatment group (23.5%) and the placebo treatment group (10.0%). With a total sample size of 420, there will be 96% power to detect

a difference of 12.5% in the other primary endpoint of clinical remission at Week 12, assuming a placebo rate at 6.0%.

- **Randomisation and Blinding (masking)**

Eligible subjects were randomised (2:1 ratio) to receive either etrasimod (2 mg once daily) or matching placebo (once daily) in a double-blind fashion. Randomisation will be stratified by (a) naïve to biologic or Janus kinase (JAK) inhibitor therapy at study entry (Yes or No), (b) Baseline corticosteroid use (Yes or No), and (c) Baseline disease activity (modified Mayo score [MMS]: 4 to 6 or 7 to 9). Randomisation was centrally implemented using an IWRS.

The studies were blinded with identical appearance of the active and placebo tablets (and bottles) and blinding was maintained unless knowledge was necessary in case of emergency medical care or regulatory reporting of SAEs.

Results of the WBC counts as well as FC and CRP were blinded to the investigators.

There appeared to be a risk for unblinding with the HR recording on the first day, for those patients with relevant HR reductions and this triggered further clarification. At request, the applicant has evaluated the subgroups of patients with clinically potentially relevant heart rate reduction on the first day with regard to the efficacy results and rates of discontinuation. However, relevant differences were not detected, and therefore, the risk of bias introduced by functional unblinding, even if it occurred, was concluded to be low.

- **Statistical methods**

For both studies, the Full Analysis Set (FAS) was used as the primary analysis population for primary and (key) secondary endpoints and consists of all randomised subjects who received at least 1 dose of study treatment. Subjects were analysed according to treatment to which they were randomised, regardless of treatment actually received.

Exploratory and additional endpoints were based on the modified Full Analysis Set (mFAS) containing all subjects who receive at least 1 dose of study treatment and have a Baseline and at least 1 post-randomisation measurement (for the corresponding endpoint). Regarding these analyses, concerns were raised, since "having no post-baseline assessment" could be influenced by the treatment and is therefore not in line with the ITT principle. This issue, which was much more relevant for study 301, is however, not considered of further concern, given that re-evaluations based on the FAS (not-excluding patients without post-baseline data) were conducted that are generally in line with the previously reported data and support (long-term) efficacy of etrasimod.

Primary analyses were furthermore restricted to subjects with actual baseline MM of 5 to 9, which was implemented in the SAP only, but not in the protocols, which is not regarded to be a relevant concern since the full FAS analysis was also presented, without changing the results.

In study 301, time to loss of response was to be summarised for the FAS with Baseline MMS 5 to 9 for subjects with an observed clinical response at Week 12. Descriptive statistics, Kaplan-Meier estimate were to be provided and the log-rank test was to be applied. If a subject does not meet the criteria for loss of response, they will be censored at the date of last dose or date of last study visit up to Week 52, whichever is later.

Subjects with a missing efficacy outcome were included in the primary analyses using the following missing data methods:

- Primary method: Single imputation as non-responder
- Sensitivity analyses: Multiple imputation under MAR, tipping point analysis, multiple imputation with CR under MNAR, and a hybrid imputation with multiple imputation (MAR) to handle

missing endoscopy data due to the COVID-19 pandemic impact and NRI for missing data not due to the COVID-19 pandemic impact.

- Supplementary analyses: mFAS analysis with data as observed, Per Protocol Set analysis (Week 12 Per Protocol Set for Week 12 endpoints and Week 52 Per Protocol Set for Week 52 endpoints).

Overall, the proposed primary analysis and primary missing data handling is acceptable and aligned to the targeted estimand.

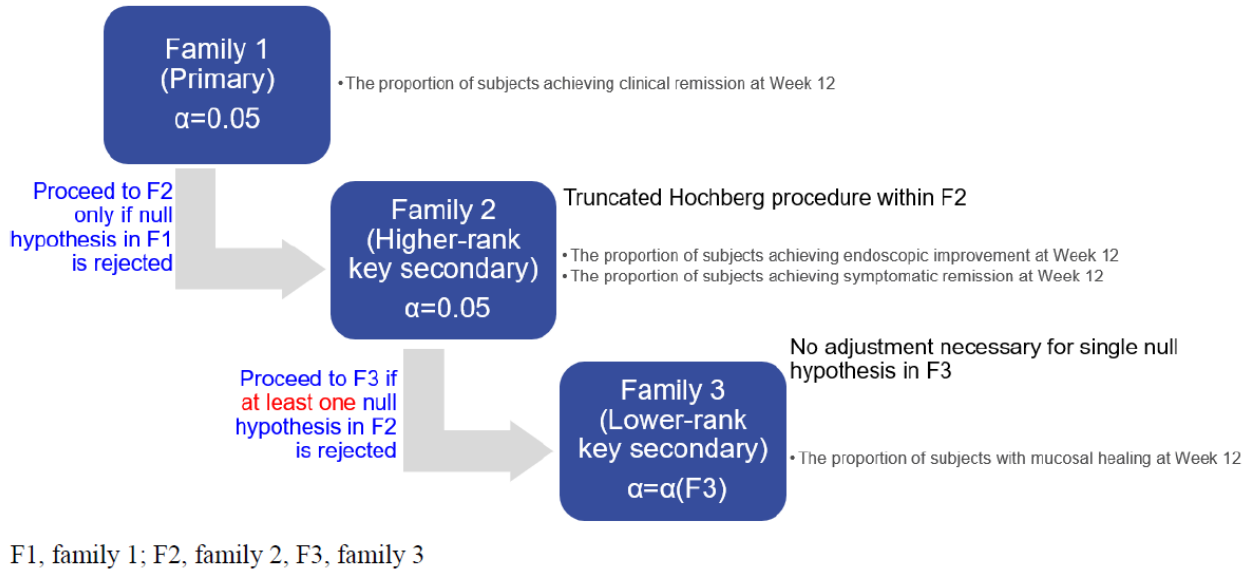
The different sensitivity analyses are to the most part supported to evaluate robustness of results. The MAR assumption may be questionable and anticonservative especially if missing data are related to treatment changes. The conducted CR imputation is agreed and supports robustness of results.

The omission of the originally planned tipping point analyses was considered acceptable. The alternative post-hoc tipping point analysis conducted is meaningful (for subjects with missing data it explores a range of plausible response probabilities for placebo and etrasimod arm) and supports robustness of results. For study 301, no tipping point could be identified and for study 302 scenarios for which conclusions on the primary analysis are overturned are implausible.

Change from Baseline endpoints (including health related QoL endpoints) were to be analysed using a mixed-effect model with repeated measures (MMRM), with factors for stratification variables, treatment, visit, treatment by visit interaction, a covariate of the corresponding Baseline, and a random subject effect. Unstructured covariance will be used. While for binary endpoints the estimand addressed is clear and agreed, no estimand was defined for continuous endpoints and application of a composite strategy as used for binary endpoints was initially not readily applicable. Regardless of the estimand targeted for continuous change from baseline endpoints (treatment policy or hypothetical) the MAR assumption underlying the MMRM analysis may not be appropriate and result in overestimation of treatment effects. Hence, re-analysis of selected continuous endpoints was conducted using placebo-based multiple imputation (J2R and CR) to handle missing data. While the new analyses (as expected) provide smaller estimates of effect size, the results of these analyses are still generally in line with the originally presented evaluations.

Evaluation based on observed cases, as foreseen for many other secondary and exploratory endpoints, is not considered appropriate for binary endpoints. Reanalysis using non-response imputation to handle missing data was conducted for exploratory/additional binary endpoints related to histology-based response and remission and the results clearly support conclusions on efficacy.

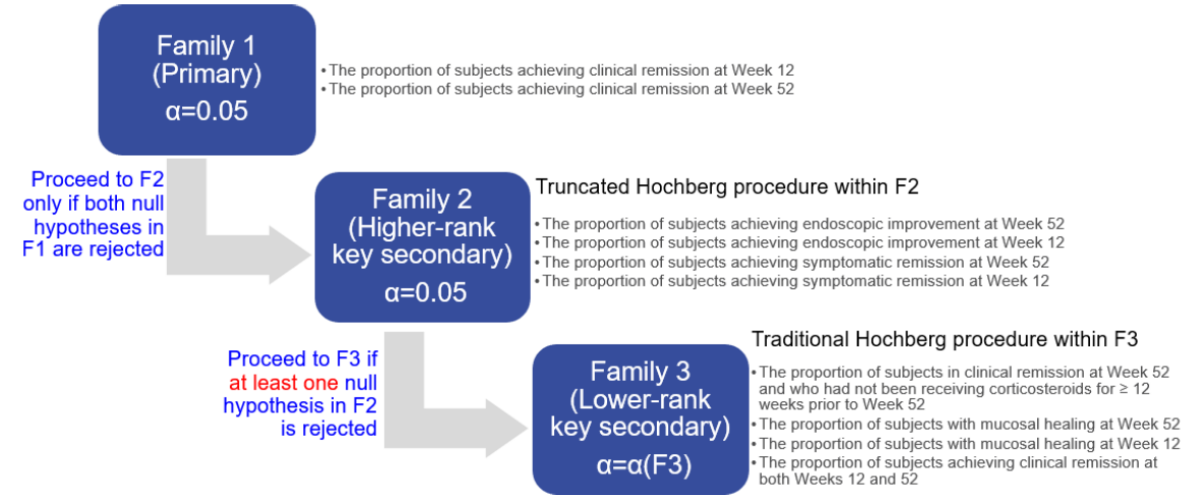
There were multiple null hypotheses for the comparison of etrasimod and placebo in the primary and key secondary endpoints in both studies. The family-wise type I error rate will be controlled at a fixed α level at 0.05 (2-sided) using the following parallel gatekeeping procedures for study 302:



F1, family 1; F2, family 2, F3, family 3

Figure 21: Statistical evaluation – Study APD334-302

For study 301, the family-wise type I error rate was to be controlled at a fixed α level at 0.05 (2-sided) using the following testing procedure. First, the whole α was to be spent on testing family 1 (F1) consisting of the co-primary endpoints. This study was to be considered as an overall success only if both of the primary null hypotheses are rejected, each at the α level. This study was to be considered as a partial success if only 1 of the 2 primary null hypotheses are rejected at α/2 if the other has p-value > α.



F1, family 1; F2, family 2, F3, family 3

Figure 22: Planned statistical evaluation – Study APD334-301

In the documentation, a discussion of study results with regard to the applied multiplicity procedure is missing, which is considered improper study reporting. However, given the results (nominal p-values; see below) it is apparent that statistical significance can be claimed for all endpoints under the pre-specified parallel gatekeeping procedure.

Results

Study APC334-301:

- **Participant flow**

The following table shows the patient disposition in the trial. Of more than 800 patients screened, there were almost 50% screen failures, and finally 433 patients were randomised.

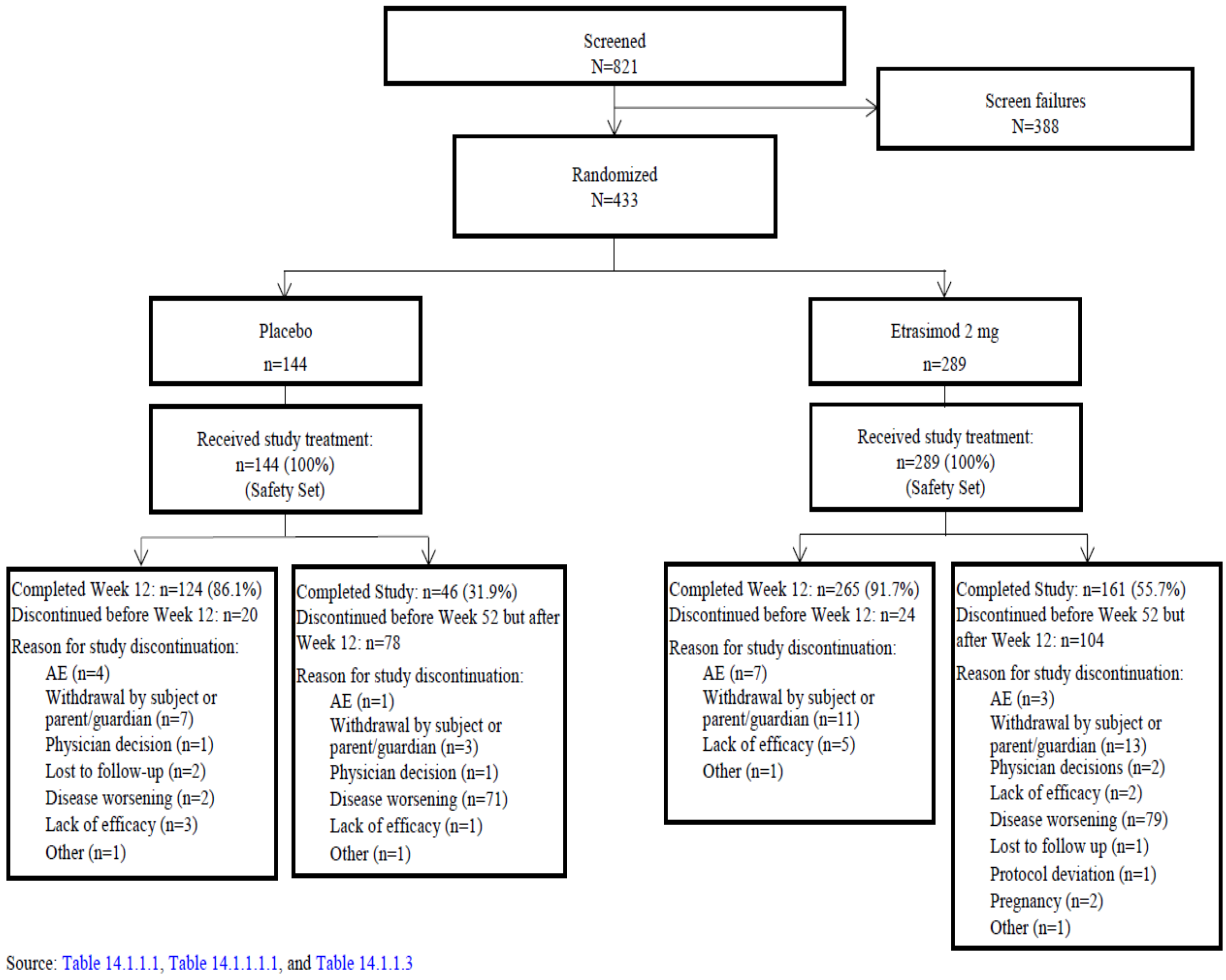


Figure 23: Subject disposition, study APD334-301

Of the overall number of 433 patients treated, there was a substantial proportion of patients discontinuing treatment as well as the study during the course of the trial. While the discontinuations before week 12 were only 13.9% and 8.3% in the placebo and active study group, the figures already indicate a differential drop-out during the 12-week "induction" period, which was not as obvious in study 302. During the long-term treatment period from week 13 to 52, the number of overall discontinuations amounted to 78 further patients in the placebo groups (54.2%), while in the etrasimod group the additional discontinuations were 104 (36.0%) indicating a relevant difference. This difference can be mainly attributed to cases of lack of efficacy and/or disease worsening. The high and differential discontinuation rates make on one hand the interpretation of the results challenging but do also obviously indicate efficacy of the active treatment.

- **Recruitment**

The study started on 13th June 2019 with the first subject enrolled and was completed on 16th February 2022. The statistical analysis plan was finalised and is dated 19th January 2022.

- **Conduct of the study**

The original study protocol dated 19th December 2018 underwent 3 major (global) amendments, and 3 minor (regional) amendments. As already mentioned, the potentially critical amendment was the introduction of different entry criteria for the OLE study which was introduced with amendment 2.0 in December 2019.

- **Baseline data**

Overall, demographic and baseline characteristics, including prior and concomitant medications for UC, were generally well balanced between etrasimod and placebo treatment groups. The mean (SD) age at consent was 41.2 (13.97) and 38.9 (14.04) years for etrasimod and placebo groups, respectively. There was 1 subject < 18 years (0 etrasimod; 1 placebo). The percentage of female subjects was higher in the etrasimod group (47.4%) compared with the placebo group (38.9%). The main characteristics are displayed in the following table:

Table 27: Demographic and other baseline characteristics – Study APD334-301

	Statistic	Placebo (N = 144)	Etrasimod 2 mg (N = 289)	Total (N = 433)
Age on consent (years)	n	144	289	433
	Mean (SD)	38.9 (14.04)	41.2 (13.97)	40.4 (14.02)
	Median	35.5	40.0	38.0
	Min – Max	17 – 78	18 – 78	17 – 78
< 18	n (%)	1 (0.7)	0	1 (0.2)
18 to 64	n (%)	133 (92.4)	272 (94.1)	405 (93.5)
≥ 65	n (%)	10 (6.9)	17 (5.9)	27 (6.2)
≥ 75	n (%)	1 (0.7)	2 (0.7)	3 (0.7)
Sex				
Male	n (%)	88 (61.1)	152 (52.6)	240 (55.4)
Female	n (%)	56 (38.9)	137 (47.4)	193 (44.6)
Woman of Childbearing Potential				
Yes	n (%)	40 (27.8)	90 (31.1)	130 (30.0)
No	n (%)	16 (11.1)	47 (16.3)	63 (14.5)
BMI (kg/m^2)	n	144	289	433
	Mean (SD)	25.26 (5.367)	25.40 (5.517)	25.35 (5.462)
	Median	25.19	24.48	24.65
	Min - Max	16.2 – 49.7	13.0 – 51.1	13.0 – 51.1

The vast majority of patients were white (88.9% overall), and only 2.1%, 7.2%, and 0.9% were assigned to be of other race (Black or African American, Asian, and American Indian or Alaska Native, respectively) without differences in the treatment groups. The was majority of patients were assigned to be non-Hispanic or Latino (94.9%), 4.4% Hispanic or Latino, and 0.5% and 0.2% with not reported or unknown ethnicity (no obvious differences between the treatment groups).

18.2% of the population were recruited from North America, 8.5% from Western Europe, and the vast majority (61.7%) from Eastern Europe (other regions were given with 11.5%).

The baseline disease characteristics are given in the following table:

Table 28: Baseline Characteristics Related to Ulcerative Colitis (Full Analysis Set) – Study APD334-301

	Statistic	Placebo (N = 144)	Etrasimod 2 mg (N = 289)	Total (N = 433)
Baseline MMS	n (%)	144 (100.0)	289 (100.0)	433 (100.0)
	Mean (SD)	6.7 (1.15)	6.7 (1.20)	6.7 (1.18)
	Median	7.0	7.0	7.0
	Min - Max	4.0 - 9.0	4.0 - 9.0	4.0 - 9.0
Baseline RB subscore				
1	n (%)	57 (39.6)	106 (36.7)	163 (37.6)
2	n (%)	83 (57.6)	160 (55.4)	243 (56.1)
3	n (%)	4 (2.8)	23 (8.0)	27 (6.2)
Baseline SF subscore				
0	n (%)	2 (1.4)	4 (1.4)	6 (1.4)
1	n (%)	16 (11.1)	28 (9.7)	44 (10.2)
2	n (%)	45 (31.3)	91 (31.5)	136 (31.4)
3	n (%)	81 (56.3)	166 (57.4)	247 (57.0)
Baseline ES subscore				
2	n (%)	56 (38.9)	126 (43.6)	182 (42.0)
3	n (%)	88 (61.1)	163 (56.4)	251 (58.0)
Baseline PGA				
0	n (%)	1 (0.7)	3 (1.0)	4 (0.9)
1	n (%)	4 (2.8)	8 (2.8)	12 (2.8)
2	n (%)	84 (58.3)	181 (62.6)	265 (61.2)
3	n (%)	53 (36.8)	95 (32.9)	148 (34.2)
Missing	n (%)	2 (1.4)	2 (0.7)	4 (0.9)
Baseline total Mayo Clinic score	n (%)	142 (98.6)	287 (99.3)	429 (99.1)
	Mean (SD)	9.0 (1.43)	9.0 (1.50)	9.0 (1.48)
	Median	9.0	9.0	9.0
	Min - Max	6.0 - 12.0	5.0 - 12.0	5.0 - 12.0
Duration of ulcerative colitis (years)[b]	n	144	289	433
	Mean (SD)	5.9 (5.52)	7.5 (8.00)	6.9 (7.30)
	Median	4.5	4.7	4.6
	Min - Max	0.2 - 30.8	0.3 - 37.9	0.2 - 37.9
Naive to biologic or JAK inhibitor therapy – Reported[c]				
No	n (%)	55 (38.2)	108 (37.4)	163 (37.6)
Yes	n (%)	89 (61.8)	181 (62.6)	270 (62.4)

	Statistic	Placebo (N = 144)	Etrasimod 2 mg (N = 289)	Total (N = 433)
Naive to biologic or JAK inhibitor therapy - Actual[c]				
No	n (%)	45 (31.3)	84 (29.1)	129 (29.8)
Yes	n (%)	99 (68.8)	205 (70.9)	304 (70.2)
Naive to biologic or JAK inhibitor therapy - Difference				
Report=Yes and Actual=No	n (%)	2 (1.4)	6 (2.1)	8 (1.8)
Report=No and Actual=Yes	n (%)	12 (8.3)	30 (10.4)	42 (9.7)
Baseline corticosteroid use - Reported[c,d]				
No	n (%)	98 (68.1)	193 (66.8)	291 (67.2)
Yes	n (%)	46 (31.9)	96 (33.2)	142 (32.8)
Baseline corticosteroid use - Actual[c,d]				
No	n (%)	102 (70.8)	196 (67.8)	298 (68.8)
Yes	n (%)	42 (29.2)	93 (32.2)	135 (31.2)
Baseline corticosteroid use - Difference[d]				
Report=Yes and Actual=No	n (%)	5 (3.5)	7 (2.4)	12 (2.8)
Report=No and Actual=Yes	n (%)	1 (0.7)	4 (1.4)	5 (1.2)
Baseline MMS Group - Reported[c]				
4 to 6	n (%)	58 (40.3)	116 (40.1)	174 (40.2)
7 to 9	n (%)	86 (59.7)	173 (59.9)	259 (59.8)
Baseline MMS Group - Actual[c]				
4 to 6	n (%)	57 (39.6)	113 (39.1)	170 (39.3)
7 to 9	n (%)	87 (60.4)	176 (60.9)	263 (60.7)
5 to 9	n (%)	135 (93.8)	274 (94.8)	409 (94.5)
Baseline MMS Group - Difference				
Report=4 to 6 and Actual=7 to 9	n (%)	1 (0.7)	4 (1.4)	5 (1.2)
Report=7 to 9 and Actual=4 to 6	n (%)	0	1 (0.3)	1 (0.2)
Prior failure of oral 5-ASA only				
No	n (%)	115 (79.9)	244 (84.4)	359 (82.9)
Yes	n (%)	29 (20.1)	45 (15.6)	74 (17.1)
Prior failure of anti-TNF				
No	n (%)	114 (79.2)	239 (82.7)	353 (81.5)
Yes	n (%)	30 (20.8)	50 (17.3)	80 (18.5)

The overall disease severity indicated severe disease in the majority of the patients (almost 60%). The duration of the disease was almost a mean of 7 years, however, with a very wide range, leading to a median of 4.7 years, indicating that the majority of patients had a less than 5-year history of the disease. The number of patients having received 5-ASA compounds only was 17%, and the number of patients with proctitis was relatively low (8.3%). Patients with MMS=4 (and not analysed in the primary analyses) were 5.5% overall. The subgroup analyses for these patients in comparison to the primary analysis population was presented at request and was in accordance with the overall results.

The number of exacerbations within the last 12 months is given as 90%, but only 68.6% were declared as ongoing at the time of inclusion and could be attributed to insufficient definitions of "exacerbation" and their recording. It remains also unclear how many patients were recruited based on a "historically only" failed treatment, or whether failure to respond to other treatments was related to the current

(ongoing) exacerbation. At request, no relevant subgroup could be identified for these criteria since these data were not systematically recorded.

The discrepancies between the CRF- and IWRS related baseline characteristics were sufficiently explained by the applicant.

The treatment history indicated that more than 2/3 of the population had used 5-ASA compounds, and ¾ had used corticosteroids, while for thiopurines, anti-TNFs, anti-integrins, anti-interleukin 12/23, and JAK inhibitors, the previous use was 36%, 21%, 11%, 1.6%, and 6.7%.

Use of concomitant medication was restricted during the study, and almost 90% of the population used additional concomitant UC medication, mainly consisting of 5-ASA products, and local and systemic corticosteroids (systemic corticosteroids were used in 28%). Small percentages of the patients used antidiarrhoeals such as loperamide or diosmectite, and bacterial preparations.

- **Numbers analysed**

The number of patients included in the trial was 433, of which 144 were randomised to placebo, and 289 to etrasimod. The analysed sets are displayed in the following table:

Table 29: Analysis Sets (Randomised Set), Study APD334-301

Analysis Sets [a]	Placebo (N = 144) n (%)	Etrasimod 2 mg (N = 289) n (%)	Total (N = 433) n (%)
Full Analysis Set[b]	144 (100.0)	289 (100.0)	433 (100.0)
Full Analysis Set with MMS 5-9	135 (93.8)	274 (94.8)	409 (94.5)
Modified Full Analysis Set[c]			
RB + SF	141 (97.9)	283 (97.9)	424 (97.9)
ES	130 (90.3)	267 (92.4)	397 (91.7)
MMS	124 (86.1)	263 (91.0)	387 (89.4)
ES + Geboes Index	124 (86.1)	257 (88.9)	381 (88.0)
Week 12 Per Protocol Set[d]	128 (88.9)	266 (92.0)	394 (91.0)
Week 52 Per Protocol Set[e]	118 (81.9)	247 (85.5)	365 (84.3)
Safety Set[f]	144 (100.0)	289 (100.0)	433 (100.0)
Pharmacokinetic Set[g]	0	287 (99.3)	287 (66.3)
Biomarker Analysis Set[h]	98 (68.1)	185 (64.0)	283 (65.4)

[a] Subjects are counted in the Safety Set according to treatment received. For all other analysis sets, subjects are counted according to treatment planned.
[b] The FAS includes all randomized subjects who receive at least 1 dose of study treatment.
[c] The mFAS includes all subjects who are randomized, receive at least 1 dose of study treatment, and have a Baseline and at least 1 post-randomization measurement. The number of subjects included in mFAS can vary depending on outcome measure.
[d] The Week 12 Per Protocol Set includes all subjects in the FAS who adhere to the protocol in the 12-week treatment period and complete Week 12.
[e] The Week 52 Per Protocol Set includes all subjects in the FAS who adhere to the protocol in the 52-week treatment period and complete Week 52.
[f] The Safety Set includes all subjects who are randomized and received at least 1 dose of study treatment.
[g] The Pharmacokinetic Set includes all subjects in the Safety Set with at least 1 quantifiable postdose etrasimod concentration measurement which is not impacted by protocol violations or events with potential to affect the PK concentration.
[h] The Biomarker Analysis Set includes all randomized subjects with a Baseline MMS 5 to 9 and who received at least 1 dose of study treatment, had a Baseline and at least one post-randomization exploratory biomarker measurement, and additionally, for EpiontisID, gave consent for the pharmacogenetic analysis.
Note: Percentages are based on the number of subjects randomized.
Sources: Table 14.1.1.4; Table 14.2.1.1, Table 14.2.33.16; Study APD334-301 EB Table 2

The Modified FAS excludes about 2% of the patients from the analysis of the symptoms (which could be considered acceptable since the number is very low), but 8.3% for the endoscopic evaluation, 10.6% from the MMS based evaluation, and 12% from the endoscopy plus histology evaluation. Some other endpoints even include less than the mFAS population given above. The re-evaluations requested, however, have demonstrated robustness of the results.

The number of protocol violations was overall relatively high (about 50%), and in 14% of the violations this was impacted by the Covid-19 pandemic. The number is higher than in study 302 (see below), but can be related to the longer study duration.

- **Outcomes and estimation**

The following table displays the results of the primary as well as the "key secondary" endpoints from the study, based on the FAS MMS 5-9 population:

Table 30: Overview of Primary and Key Secondary Endpoint Results at Week 12 – Using Reported Randomisation Strata – Full Analysis Set and Actual Baseline MMS 5 to 9. Study 301

Endpoint (No. of responders)		**Study APD334-301**		
		Placebo N = 135 n (%)	**Etrasimod 2 mg N =274 n (%)**	**% Difference (2-sided p-value)[a]**
Primary endpoints	Clinical remission at Week 12	10 (7.4)	74 (27.0)	19.75 (12.88, 26.63) p=0.001
	Clinical remission at week 52	9 (6.7)	88 (32.1)	25.39 (18.42, 32.36) p<0.001
Key secondary endpoints	Endoscopic improvement at Week 12	19 (14.1)	96 (35.0)	21.18 (13.03, 29.32) P<0.001
	Endoscopic improvement at Week 52	14 (10.4)	102 (37.2)	26.69 (18.99, 34.39) <0.001
	Symptomatic remission at Week 12	29 (21.5)	126 (46.0)	24.55 (15.46, 33.63) P<0.001
	Symptomatic remission at week 52	25 (18.5)	119 (43.4)	24.89 (16.17, 33.60) P<0.001
	Mucosal healing at Week 12	6 (4.4)	58 (21.2)	16.88 (10.78, 22.98) P<0.001

Endpoint (No. of responders)		**Study APD334-301**		
	Mucosal healing at Week 52	11 (8.1)	73 (26.6)	18.39 (11.39, 25.39) P<0.001
Key sec.EPs week 52 only	Corticosteroid free Clinical Remission	9 (6.7)	88 (32.1)	25.39 (18.42, 32.36) P<0.001
	Sustained Clinical remission (week 12 and week 52)	3 (2.2)	49 (17.9)	15.84 10.66, 21.03) P<0.001

In the supplementary analyses of the primary and key secondary endpoints, the primary model was repeated using the mFAS (with data as observed) and Per Protocol Set in subjects with Baseline MMS 5 to 9. Analysis with the primary model was repeated for the primary endpoint using the FAS with Baseline MMS 4 to 9. The multiple imputations, tipping point analysis, mFAS and Per Protocol Set analyses was repeated for all subjects in the analysis set with Baseline MMS 4 to 9 for the primary endpoint.

At request, further analyses for the supplementary and sensitivity analyses were presented which were in line with the initial presentations.

The applicant has also conducted several subgroup analyses, including factors like age, sex, race, baseline corticosteroid use, pre-treatment with biologics/JAKs, pre-treatment with 5-ASA only, baseline MMS, baseline FC, duration of UC and extent of disease. These analyses were generally in line with the primary evaluation, with slight deviations (without demonstrating statistically significant results) in some of the subgroups, which included less patients, such as some race categories, prior treatment failure of anti-TNF/JAK, and age above/below 65 years of age The point estimates for these analyses were, however, always, or at least in their large majority, in line with a positive effect of treatment.

It has also been noted that for the evaluation of the corticosteroid-free clinical remission endpoint, an outdated definition (according to earlier protocol versions) of "not received corticosteroids for ≥ 12 weeks in the 40-week treatment period has been used (as of the CSR). Adequate clarification and re-analysis was provided. At request, the applicant also demonstrated a corticosteroid sparing effect in study 301, which showed that both the duration and doses administered could be reduced on active treatment as compared to placebo supporting the results of the "corticosteroid-free" endpoints.

As demonstrated in a subgroup analysis of corticosteroid-free clinical remission at week 52 (FAS MMS 5-9 population), the proportion of patients achieving adequately defined corticosteroid-free clinical remission at week 52 in the subgroup of patients who used corticosteroids at baseline was significantly higher in etrasimod group (27/87 (31.0%) vs 3/40 (7.5%), % difference (95% CI) 23.05 (10.20, 35.90), p<0.001).

The evaluations of the "other" and "exploratory" secondary endpoints were generally in line with the primary evaluations, and only a selection of these is shown in the following:

Table 31: Selected Secondary ("other secondary" and "exploratory") efficacy endpoints – FAS population (or mFAS population as indicated) with MMS 5-9 – Study APD334-301; week 12 evaluation.

Endpoint Week 12	**Study APD334-301**		
	Placebo **N = 135** **n (%)**	**Etrasimod 2 mg** **N = 274** **n (%)**	**% Difference** **(2-sided p-value)[a]**
Clinical response	46 (34.1%)	171 (62.4%)	28.27 (18.51, 38.02) <0.001
Endoscopic normalisation	6 (4.4)	40 (14.6)	10.23 (4.73, 15.73) <0.001
Endoscopic normalisation and histological remission	2 (1.5)	29 (10.6)	9.15 (4.96, 13.35) <0.001
mFAS	N=114	N=244	
Clinical Remission (with TMS)	8 (7.0)	63 (25.8)	18.99 (11.68, 26.30) <0.001
Clinical Response (with TMS)	44 (38.6)	159 (65-2)	26.50 (15.84, 37.15) <0.001
mFAS	N=108	N=228	
Abdominal pain (Change from baseline NRS, mean)	-1.1	-2.2	-0.80 (-1.37,-0.23) 0.006
mFAS	N=109	N=227	
Urgency (Change from BL in NRS, mean)	-1.6	-2.9	-1.27 (-1.97,-0.58) <0.001

Table 32: Selected Secondary ("other secondary" and "exploratory") efficacy endpoints – FAS (or mFAS as indicated) population with MMS 5-9 – Study APD334-301; week 52 evaluation.

Endpoint at week 52	**Study APD334-301**		
FAS population	**Placebo** **N = 135** **n (%)**	**Etrasimod 2 mg** **N = 274** **n (%)**	**% Difference** **(2-sided p-value)[a]**
Clinical response	31 (23.0%)	132 (48.2%)	24.93 (15.79, 34.07)) <0.001
Endoscopic normalisation	8 (5.9)	72 (26.3)	20.39 (13.79, 26.98) <0.001
Endoscopic normalisation and histological remission	7 (5.2)	50 (18.2)	13.11 (7.21, 19.01) <0.001
Corticosteroid-free endoscopic improvement	14 (10.4)	101 (36.9)	26.35 (18.65, 34.04) <0.001
Corticosteroid-free symptomatic remission	25 (18.5)	119 (43.4)	24.89 (16.17, 33.60) <0.001
4-week corticosteroid free clinical remission	(n=40) 3 (7.5)	n=87) 27 (31.0)	23.05 (10.20, 35.90) <0.001
mFAS population	N=38	N=152	

Endpoint at week 52	Study APD334-301		
Clinical Remission (with TMS)	8 (21.1)	78 (51.3)	32.62 (17.35, 47.90) <0.001
mFAS population	N=36	N=150	
Clinical Response (with TMS)	29 (80.6)	126 (84.0)	2.84 (-11.44, 17.13) 0.696
	N=38	N=147	
Histologic improvement (Geboes)	23 (60.5)	106 (72.1)	11.63 (-6.16, 29.42) 0.200

Table 33: Secondary ("other secondary" and "exploratory") efficacy endpoints – FAS population with MMS 5-9 – Study APD334-301; combined week 12/52 evaluation.

Endpoint at week 12 and 52	Study APD334-301		
	Placebo **N = 135** **n (%)**	**Etrasimod 2 mg** **N = 274** **n (%)**	**% Difference** **(2-sided p-value)[a]**
Clinical Response at week 12 and 52	25 (18.5)	123 (44.9)	26.16 (17.48, 34.84) <0.001
Mucosal healing at week 12 and 52	3 (2.2)	37 (13.5%)	11.32 (6.49, 16.14) <0.001
Endoscopic normalisation at week 12 and 52	2 (1.5)	29 (10.6)	9.16 (4.93, 13.38) <0.001
Clinical remission at week 12 and week 52	3 (2.2)	49 (17.9)	15.84 10.66, 21.03) <0.001
Clinical remission wk 52 in those in clinical response at wk 12	8 (27.4)	84 (49.1)	31.86 (18.45, 45.28) <0.001

The above table on the combined evaluation of the two time-points is considered most relevant in determining the fate of the patients in the long term and hence receive a clearer depiction of the "maintenance of effect" in the stricter sense. For the clinical response endpoint, this means that of the placebo group, of the 46 patients achieving response at week 12, 25 have maintained their response also at week 52 (54%), while in the active treatment group, of the 171 with response at week 12, 123 have maintained their response (71,9%) The rates for the following endpoints for the placebo and active treatment groups are also given as:

- Mucosal healing, (6 patients at week 12 of which 3 maintained their mucosal healing (50%); and 58 patients of which 37 maintained mucosal healing (63.8%).
- Endoscopic normalisation (6 at week 12 of which 2 would maintain it (33.3%), and 40 at week 12 of which 29 could maintain it (72.5%).
- Clinical remission (10 patients at week 12, of which 3 could maintain it (30.0%), and 74 at week 12, of which 49 could maintain it (66.2%).

The evaluation of the symptomatic remission and complete symptomatic remission endpoints over the different time-points was generally in line with the above evaluations, indicating statistically significant results from 2 and 4 weeks onwards, respectively for these two endpoints.

At request, the applicant has shown further data on the time-course of response and remission: In those patients being in "response" at week 12, it was shown that about 36% achieved remission (clinical remission) at week 52 (while this was achieved only by about 14% in those on placebo). The proportion of patients that remained in "clinical response" (excluding those patients in remission) up to week 52 was similar between the treatment groups (about 10%). Contrary to this, the percentage of patients who lost their response (including remission) between week 12 and week 52 was 46% in the placebo, and 28% in the etrasimod group.

Mean (SD) and median time to loss of response was 268.3 (73.29) days and 287.0 (range: 13-592) days, respectively, in the etrasimod group and 237.1 (98.82) days and 285.0 (range: 25-370) days, respectively, in the placebo group (2-sided p-value = 0.099).

The time-course of response is also reflected in the occurrence of "non-response" during weeks 13-52: At Week 52 in study APD334-301, the most frequent reason for non-response (ranging from 45.1% to 61.1% among all non-responders at Week 52) was those with an intercurrent event (IE) of treatment discontinuation due to a qualified reason (ie, lack of efficacy, disease worsening, or AE related to UC), with disease worsening being the most common of the 3 reasons. The second most common type of non-responders was the true/actual non-responders (ranging from 21.4% to 36.9%). Although this observation does not challenge the conclusion that there is indeed a long-term effect vs placebo, it complicates the estimation of the size of this effect. However, despite these high rates of IEs together with the above given additional analyses on time-course of response, the results satisfactorily support long-term efficacy.

There was no improvement in EIMs at Week 12 and Week 52 with etrasimod compared with placebo in subjects with EIMs at Baseline.

There was a statistically significant change in IBDQ scores, both at week 12 and week 52. For the other instruments used for the evaluation of Quality of Life (SF 36 and WPAI-UC), overall significance could not be shown, but relevant changes could be seen in subscales. Overall, there was a relatively high dependency of the results on the choice if imputation method.

High-sensitivity CRP was reduced in both etrasimod and placebo groups and there was a significant difference between groups only for the 12-week evaluation of study 302. The applicant claims that this this was likely due to the skewed distribution of the data, which can be accepted.

Levels of faecal calprotectin began to decrease in subjects treated with etrasimod as early as Week 2. Subjects treated with etrasimod achieved a significantly greater faecal calprotectin change from Baseline at Week 12 (in study 302, this was, however, dependent on the imputation method) but no statistically significant difference at Week 52 compared to placebo was seen, which was attributed to the skewed distribution of the data by the applicant (due to the early discontinuations).

The applicant conducted only few supplementary ad hoc analyses of Endoscopic Improvement, Symptomatic Remission, Mucosal Healing, Sustained Remission and Corticosteroid-Free Clinical Remission at Week 52 after excluding subjects who only failed oral 5-ASAs in prior treatment of UC and/or subjects with isolated proctitis. At request, the applicant has also explored the results in a population with exclusion of patients having been pre-treated with 5-ASA products only, or of those having isolated proctitis, or both. Although in the combined exclusion statistical significance was no longer shown, the magnitude of effect appeared to be stable when compared between the subgroups, which was considered reassuring.

The primary endpoint of composite clinical remission was not analysed in this way, and data are not presented for FAS MMS 5-9, however, it is not expected that those results would significantly deviate or change the overall conclusions.

Ad hoc supplementary analyses – FAS population MMS 4-9 Except Subjects who Only Failed Prior Oral 5-ASA and/or had Isolated Proctitis Based on Central Read - Study APD334-301

Table 34: Ad hoc supplementary analyses – FAS population MMS 4-9 Except Subjects who Only Failed Prior Oral 5-ASA and/or had Isolated Proctitis Based on Central Read - Study APD334-301

Study APD334-301				
		Placebo N = 107 n (%)	**Etrasimod 2 mg N = 225 n (%)**	**% Difference (2-sided p-value)**
Endoscopic improvement	Week 12	19 (17.8)	72 (32.0)	14.82 (5.25, 24.39), P=0.0024
	Week 52	14 (13.1)	80 (35.6)	23.18 (14.30, 32.05), P<0.001
Symptomatic remission	Week 12	24 (22.4)	96 (42.7)	19.76 (9.51, 30.02), P<0.001
	Week 52	23 (21.5)	91 (40.4)	19.09 (9.12, 29.07), P<0.001
Mucosal healing	Week 12	6 (5.6)	43 (19.1)	13.87 (6.91, 20.82), P <0.001
	Week 52	12 (11.2)	58 (25.8)	15.18 (6.79, 23.57), P<0.001
Sustained clinical remission	Both Weeks 12 and 52	3 (2.8)	36 (16.0)	13.78 (7.97, 19.60), P<0.001

Additional supplement analyses were also provided for corticosteroid free endoscopic improvement, corticosteroid free symptomatic remission and were generally in accordance with the overall results

Etrasimod was superior to placebo in achieving another ad hoc composite endpoint of endoscopic normalisation and histologic remission at both weeks 12 and 52 (10.6% vs 1.5% at week 12 and 18.2% vs 5.2% at week 52, both p<0.001).

Results

Study APC334-302:

Participant flow

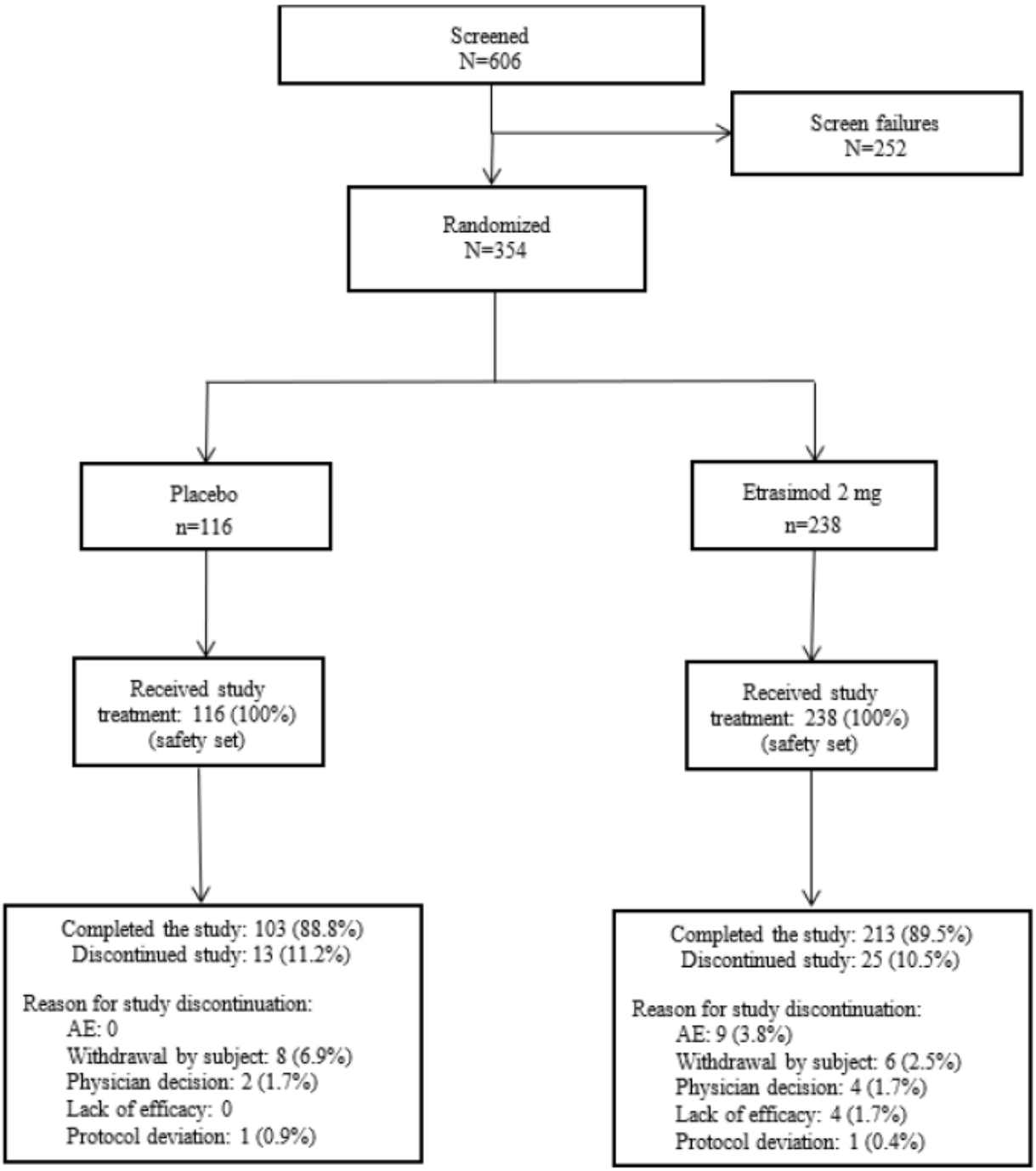


Figure 24: Subject disposition, Study APD334-302

It is to be noted that the figure above misses 2 subjects in the placebo group, which discontinued to "lost-to follow-up" and "other" reasons (1 (0.9%) each), as well as 1 subject in the etrasimod group with "other" reason for discontinuation. As can be seen, the number of discontinuations is relevantly lower than in study 301 (at the 12 week time-point). Overall, the discontinuation rates (for the 12-week period) are quite similar to study 301.

Of the 354 patients randomised, 319 (90.1%) completed the treatment, and 11 (9.5%) and 24 (10.1%) discontinued treatment prematurely. The reasons for withdrawal of treatment in the placebo and etrasimod groups were AEs (1 (0.9%) and 11 (4.6%)), withdrawal by subject/guardian (6 (5.2%) and 5 (2.1%)), physician decision (2 (1.7%) and 3 (1.3%), lack of efficacy (0 and 3 (1.3%), lost-to follow-up (1 (0.9%) and 0, and protocol deviation (1 (0.9% and 2 (0.4%).

Recruitment

The first subject was enrolled on 15th September 2020, and the primary completion date is given as 05th November 2021, and the Study completion date as 07th December 2021.

The Statistical Analysis Plan is dated 19th January 2022

Conduct of the study

The original protocol, dated 19 December 2018, was amended 3 times globally. In addition to the global amendments, region-specific amendments were generated for VHP countries. Submission contains altogether 10 versions of the protocol. No amendments of concern were detected.

Baseline data

Overall, demographic and Baseline characteristics, including prior and concomitant medications for UC, were generally well balanced between etrasimod and placebo treatment groups. The following tables show the baseline characteristics with regard to age, sex, BMI, and race/ethnicity, as well as according to medical history and prior treatment. The following table show the baseline characteristics in detail:

Table 35: Demographic and Baseline Characteristics - Full Analysis Set – Study APD334-302

	Statistic	Placebo (N=116)	Etrasimod 2 mg (N=238)	Total (N=354)
Age on consent (years)	n	116	238	354
	Mean (SD)	40.4 (13.28)	40.3 (13.49)	40.4 (13.40)
	Median	38.0	37.5	38.0
	Min - Max	17 - 72	16 - 73	16 - 73
< 18	n (%)	1 (0.9)	1 (0.4)	2 (0.6)
18 to 64	n (%)	109 (94.0)	225 (94.5)	334 (94.4)
≥ 65	n (%)	6 (5.2)	12(5.0)	18 (5.1)
≥ 75	n (%)	0	0	0
Sex				
Male	n (%)	73 (62.9)	135(56.7)	208 (58.8)
Female	n (%)	43 (37.1)	103(43.3)	146 (41.2)
Woman of Childbearing Potential				
Yes	n (%)	30 (25.9)	75 (31.5)	105 (29.7)
No	n (%)	13 (11.2)	28 (11.8)	41 (11.6)
BMI (kg/m^2)	n	116	238	354
	Mean (SD)	25.18 (4.405)	24.27 (4.823)	24.57 (4.703)
	Median	24.34	23.49	23.81
	Min - Max	15.4 - 39.1	15.8 - 40.4	15.4 - 40.4

With regard to the category of race, 75.9% and 73.9% of the participants were rated to be white, 2 (1.7% and 0.8%) in each group were Black or African American, 25 (2.16%) and 47 (19.7%) were Asian, 1 and 6 (0.9% and 2.5%) as American Indian or Alaska Native, one patient was rated as "multiple" in the etrasimod group, and in 6 patients in the etrasimod group, race was not reported. With regard to the category "ethnicity", 9 (7.8%) and 10 (4.2%) were rated as "Hispanic or latino" whereas the rest of the patients (with the exception of one not reported and one not known in the etrasimod group) were rated as "not Hispanic or Latino".

Of the total of 354 patients, 29 (8.2%) were from North America, 27 (7.6%) from Western Europe, and 190 (53.7%) from Eastern Europe with "other" regions summing up to 108 (30.5%).

Table 36: Baseline Characteristics Related to Ulcerative Colitis - Full Analysis Set – Study 302 (selection)

	Statistic	Placebo (N=116)	Etrasimod 2 mg (N=238)	Total (N=354)
Extent of Disease - CRF				
Left-sided colitis/Proctosigmoiditis	n (%)	63 (54.3)	146 (61.3)	209 (59.0)
Pancolitis	n (%)	41 (35.3)	77 (32.4)	118 (33.3)
Proctitis	n (%)	12 (10.3)	15 (6.3)	27 (7.6)
Proctitis (Central Read)[a]	n (%)	13 (11.2)	15 (6.3)	28 (7.9)
Baseline MMS	n (%)	116 (100.0)	238 (100.0)	354 (100.0)
	Mean (SD)	6.6 (1.21)	6.6 (1.23)	6.6 (1.23)
	Median	7.0	7.0	7.0
	Min - Max	4 - 9	4 - 9	4 - 9
Baseline RB subscore				
1	n (%)	39 (33.6)	95 (39.9)	134 (37.9)
2	n (%)	70 (60.3)	135 (56.7)	205 (57.9)
3	n (%)	7 (6.0)	8 (3.4)	15 (4.2)
Baseline SF subscore				
0	n (%)	1 (0.9)	2 (0.8)	3 (0.8)
1	n (%)	15 (12.9)	33 (13.9)	48 (13.6)
2	n (%)	40 (34.5)	77 (32.4)	117 (33.1)
3	n (%)	60 (51.7)	126 (52.9)	186 (52.5)
Baseline ES subscore				
2	n (%)	56 (48.3)	109 (45.8)	165 (46.6)
3	n (%)	60 (51.7)	129 (54.2)	189 (53.4)
Baseline total Mayo Clinic score	n (%)	109 (94.0)	232 (97.5)	341 (96.3)
	Mean (SD)	8.8 (1.54)	8.7 (1.52)	8.7 (1.53)
	Median	9.0	9.0	9.0
	Min - Max	5 - 12	4 - 12	4 - 12
Duration of ulcerative colitis (years)[b]	n	116	238	354
	Mean (SD)	7.7 (7.32)	7.3 (6.61)	7.4 (6.84)
	Median	4.8	4.7	4.7
	Min - Max	0 - 35	0 - 31	0 - 35
Naïve to biologic/JAK inhibitor therapy - Reported[c]				
No	n (%)	43 (37.1)	89 (37.4)	132 (37.3)
Yes	n (%)	73 (62.9)	149 (62.6)	222 (62.7)

	Statistic	Placebo (N=116)	Etrasimod 2 mg (N=238)	Total (N=354)
Naïve to biologic/JAK inhibitor therapy - Actual[c]				
No	n (%)	39 (33.6)	79 (33.2)	118 (33.3)
Yes	n (%)	77 (66.4)	159 (66.8)	236 (66.7)
Naïve to biologic/JAK inhibitor therapy – Difference				
Report= Yes and Actual=No	n (%)	0	1 (0.4)	1 (0.3)
Report=No and Actual=Yes	n (%)	4 (3.4)	11 (4.6)	15 (4.2)
Baseline corticosteroid use - Reported[c, d]				
No	n (%)	78 (67.2)	160 (67.2)	238 (67.2)
Yes	n (%)	38 (32.8)	78 (32.8)	116 (32.8)
Baseline corticosteroid use - Actual[c, d]				
No	n (%)	82 (70.7)	173 (72.7)	255 (72.0)
Yes	n (%)	34 (29.3)	65 (27.3)	99 (28.0)
Baseline corticosteroid use - Difference [d]				
Report= Yes and Actual=No	n (%)	4 (3.4)	13 (5.5)	17 (4.8)
Report=No and Actual=Yes	n (%)	0	0	0
Baseline MMS Group - Reported[c]				
4 to 6	n (%)	53 (45.7)	108 (45.4)	161 (45.5)
7 to 9	n (%)	63 (54.3)	130 (54.6)	193 (54.5)
Baseline MMS Group - Actual[c]				
4 to 6	n (%)	53 (45.7)	109 (45.8)	162 (45.8)
7 to 9	n (%)	63 (54.3)	129 (54.2)	192 (54.2)
5 to 9	n (%)	112 (96.6)	222 (93.3)	334 (94.4)
Baseline MMS Group - Difference				
Report=4 to 6 and Actual=7 to 9	n (%)	0	0	0
Report=7 to 9 and Actual=4 to 6	n (%)	0	1 (0.4)	1 (0.3)

[a] Includes subjects with Extent of Disease reported as "No" or "Cannot be determined" in Bioclinica endoscopy data.
[b] Duration of ulcerative colitis (years) is calculated as (informed consent date – diagnosis date + 1)/365.25
[c] Reported stratum is from the IWRS and actual stratum is derived from relevant CRF pages.
[d] Corticosteroids were defined using ATC4 codes and included Budesonide.

Notes:
Percentages are based on the number of subjects in the analysis set.
Source: Table 14.1.3.3

The presentation of the detailed baseline characteristics with regard to disease severity shows that the majority of patients had and SF score of 3, and a RB score of 2. Slightly more patients had ES=3 than ES=2.

Details on prior treatment of UC is given with the following table. There were 73.3% and 71.8% of the participants in the placebo and etrasimod groups who never received a biologic or JAK inhibitor, and only 11.2% and 15.1% had a pervious treatment with more than one of these substances.

With regard to these baseline data, some discrepancies were noted by the applicant between data as of the CRFs and of the IWRS system, as well as between the ISE and the CSRs, which have been further clarified upon request, and are overall considered satisfactory.

Of note, is also the fact that 12 (10.3) 28 (11.8) patients were previously treated with 5-ASAs alone.

Table 37: Prior Treatment for Ulcerative Colitis - Full Analysis Set - Study 302.

	Statistic	Placebo (N=116) n (%)	Etrasimod 2 mg (N=238) n (%)	Total (N=354) n (%)
Prior treatment for UC				
No	n (%)	0	1 (0.4)[a]	1 (0.3)
Yes	n (%)	116 (100.0)	237 (99.6)	353 (99.7)
Category of treatment				
Oral 5-aminosalicylic acid compounds	n (%)	85 (73.3)	149 (62.6)	234 (66.1)
Corticosteroids	n (%)	98 (84.5)	177 (74.4)	275 (77.7)
Estimated use (weeks) over last 12 months	Mean (SD)	12.1 (14.47)	12.3 (14.76)	12.2 (14.63)
	Median	8.0	8.0	8.0
	Min - Max	0 - 54	0 - 52	0 - 54
Thiopurines	n (%)	49 (42.2)	89 (37.4)	138 (39.0)
Antitumor necrosis factor alpha antibodies	n (%)	29 (25.0)	57 (23.9)	86 (24.3)
Anti-integrin antibodies	n (%)	10 (8.6)	33 (13.9)	43 (12.1)
Anti-interleukin 12/23 antibodies	n (%)	4 (3.4)	5 (2.1)	9 (2.5)
JAK Inhibitors	n (%)	9 (7.8)	15 (6.3)	24 (6.8)
Other	n (%)	42 (36.2)	67 (28.2)	109 (30.8)

[a] This subject in the etrasimod group was mis-stratified for no baseline corticosteroid status which resulted in randomization to study treatment without having demonstrated an inadequate response to, loss of response to, or intolerance to a prior therapy for UC, however the subject had previously received and responded to corticosteroid treatment for UC.

Source: Table 14.1.3.4.

During the study, more than 90% received concomitant medications for ulcerative colitis, with 5-ASA products taking the main share, followed by local or systemic corticosteroid treatment. Almost 25% of the patients used systemic corticosteroids.

The number of patients with proctitis was 11.2% and 6.3% in the active and placebo groups, respectively.

Numbers analysed

The study included 354 patients altogether, of which 116 were randomised to placebo, and 238 to etrasimod. The analysed sets of patients are given in the following table:

Table 38: Analysis Sets - All Randomised Set – Study 302

Analysis Sets[a]	Placebo (N=116) n (%)	Etrasimod 2 mg (N=238) n (%)	Total (N=354) n (%)
Full Analysis Set[b]	116 (100.0)	238 (100.0)	354 (100.0)
Modified Full Analysis Set[c]			
RB + SF	110 (94.8)	232 (97.5)	342 (96.6)
ES	104 (89.7)	216 (90.8)	320 (90.4)
MMS	104 (89.7)	213 (89.5)	317 (89.5)
ES + Geboes Index	97 (83.6)	212 (89.1)	309 (87.3)
Per Protocol Set[d]	101 (87.1)	219 (92.0)	320 (90.4)
Safety Set[e]	116 (100.0)	238 (100.0)	354 (100.0)
Pharmacokinetic Set[f]	0	237 (99.6)	237 (66.9)
Biomarker Analysis Set[g]	68 (58.6)	120 (50.4)	188 (53.1)

[a] Subjects are counted in the Safety Set according to treatment received. For all other analysis sets, subjects are counted according to treatment planned.
[b]The FAS includes all randomized subjects who receive at least 1 dose of study treatment.
[c]The mFAS includes all subjects who are randomized, receive at least 1 dose of study treatment, and have a Baseline and at least 1 post-randomization measurement. The number of subjects included in mFAS can vary depending on outcome measure.
[d]The Per Protocol Set includes all subjects in the FAS who adhere to the protocol as defined in the Statistical Analysis Plan.
[e]The Safety Set includes all subjects who are randomized and receive at least 1 dose of study treatment.
[f] The Pharmacokinetic Set includes all subjects in the Safety Set with at least 1 quantifiable postdose etrasimod concentration measurement which is not impacted by protocol violations or events with potential to affect the etrasimod concentration.
[g]The Biomarker Analysis Set includes all randomized subjects with a Baseline MMS 5 to 9 and who received at least 1 dose of study treatment, had a Baseline and at least one post-randomization exploratory biomarker measurement, and additionally, for EpiontisID, gave consent for the pharmacogenetic analysis.
Notes:
Percentages are based on the number of subjects in the analysis set.
Sources: Table 14.1.1.4; Table 14.2.29.16; Study APD334-302 EB Table 1.2

Again, similar to study 301, exploratory and additional endpoints is based on the "modified FAS" population only with 5-18% of the patients not included in the analysis.

In this study, about 22% of the patients had protocol deviations which were considered important and, overall only a tiny minority of these were impacted by the Covid-19 pandemic.

Treatment compliance was generally high with 100.0% (2.93) for etrasimod and 99.5% (4.66) for placebo.

Outcomes and estimation

The following table displays the results of the primary as well as the "key secondary" endpoints from the study, based on the FAS MMS 5-9 population:

Table 39: Overview of Primary and Key Secondary Endpoint Results at Week 12 – Using Reported Randomisation Strata – Full Analysis Set and Actual Baseline MMS 5 to 9 – Study APD334-302

Endpoint		Study APD334-302		
		Placebo N = 112 n (%)	Etrasimod 2 mg N = 222 n (%)	% Difference (2-sided p-value)[a]
Primary endpoints	Clinical remission at Week 12	17 (15.2)	55 (24.8)	9.69 (1.14; 18.23) 0.026

Endpoint		Study APD334-302		
Key secondary endpoints	Endoscopic improvement at Week 12	21 (18.8)	68 (30.6)	12.11 (3.0; 21.23 0.009
	Symptomatic remission at Week 12	33 (29.5)	104 (46.8)	17.48 (6.82; 28.15 0.001
	Mucosal healing at Week 12	10 (8.9)	36 (16.2)	7.44 (0.50; 14.39) 0.036

The clinical remission rate (primary endpoint) for the full population (MMS 4-9) was 14.7% for placebo, and 26.1% for active treatment, leading to a p=0.007.

Again, sensitivity and supplementary analyses for the primary and key secondary endpoints were evaluated and showed similar results. At request, again additional sensitivity analyses were requested (including the tipping point analysis, which were finally acceptable and in line with initially presented results.

Overall it is to be noted that the magnitude of effect in this study was lower than in study 301, and for some of the key secondary endpoints statistical significance was only closely met. The applicant has evaluated the reasons for these differences and identified important baseline differences of the patient population favouring the relatively high placebo response in this study.

Subgroup analyses have been conducted similar to study 301 with the same factors. Again – and to higher extent overall – statistical significance was no longer shown, this time not only for small subgroups only, but obviously also due to the lower overall magnitude of effect. A "negative" (or zero) point estimate, not showing a benefit for the patients, however, is shown for those having been pre-treated with more than one biologic/JAP inhibitor previously and for those aged above 65. Both subgroups have been looked at again with pooled results and the 52-week evaluations, and at least for the elderly, results appear indeed attributable to the overall variability due to the different patient populations. However, a further discussion for those "heavily pre-treated" seems necessary. Again, the subgroups of patients having been pre-treated with 5-ASA compounds only showed results that were in accordance with the overall results.

The following table shows the results of the main further secondary and "other" endpoints used in the study based on the "primary" population with an entry MMS of 5-9:

Table 40: Secondary ("other secondary") efficacy endpoints – FAS population with MMS 5-9 – Study APD334-302.

Endpoint	Study APD334-302		
	Placebo **N = 112** **n (%)**	**Etrasimod 2 mg** **N = 222** **n (%)**	**% Difference** **(2-sided p-value)[a]**
Clinical response (≥1 point and ≥30% decrease in MMS, ≥ 1-point decrease RB subscore or absolute RB subscore ≤ 1)	46 (41.1%)	138 (62.2%)	21.23 (10.18, 32.29) P<0.001
Endoscopic normalisation ES=0	9 (8.0)	38 (17.1)	9.24 (2.27, 16.20) P=0.009
Symptomatic remission Week 2	12 (10.7)	36 (16.2)	5.85 (−1.42, 13.13) P=0.115
Symptomatic remission Week 4	18 (16.1)	61 (27.5)	11.83 (3.19, 20.47) P=0.007

Endpoint	Study APD334-302		
Symptomatic remission Week 8	27 (24.1)	86 (38.7)	14.84 (4.98, 24.69) P=0.003
Complete symptomatic remission (RB=0,SF=0) Week 2	2 (1.8)	10 (4.5)	2.83 (−0.81, 6.48) P=0.128
Complete symptomatic remission (RB=0,SF=0) Week 4	4 (3.6)	26 (11.7)	8.32 (3.01, 13.64) P=0.002
Complete symptomatic remission (RB=0,SF=0) Week 8	8 (7.1)	31 (14.0)	7.06 (0.62, 13.49) p=0.032
Complete symptomatic remission (RB=0,SF=0) Week 12	10 (8.9)	40 (18.0)	9.18 (1.82, 16.54) p=0.014
Non-invasive clinical response (≥ 30% decrease in composite RB/SF, and a ≥ 1-point decrease in RB, or absolute RB subscore ≤1) Week 2	27 (24.1)	87 (39.2)	15.55 (5.65, 25.46) P=0.002
Non-invasive clinical response Week 4	46 (41.1)	124 (55.9)	14.98 (4.05, 25.91) P=0.007
Non-invasive clinical response Week 8	51 (45.5)	151 (68.0)	22.60 (11.95, 33.25) p<0.001
Non-invasive clinical response Week 12	56 (50.0)	150 (67.6)	17.58 (6.70, 28.47) P=0.002
Symptomatic response (≥ 30% decrease in RB/SF composite) Week 2	27 (24.1)	88 (39.6)	15.99 (6.07, 25.91) P=0.002
Symptomatic response Week 4	46 (41.1)	125 (56.3)	15.45 (4.54, 26.36) P=0.006
Symptomatic response Week 8	52 (46.4)	152 (68.5)	22.14 (11.43, 32.85) P<0.001
Symptomatic response Week 12	56 (50.0)	152 (68.5)	18.49 (7.65, 29.33) P<0.001
mFAS	N=91	N=177	
Remission (using TMS≤ 2 points an no subscore >1)	7 (7.7)	37 (20.9)	13.27 (5.44, 21.11) P<0.001
Clinical response (using TMS with ≥ 3-point and ≥ 30% decrease of TMS and a ≥ 1-point decrease in RB subscore or an absolute RB subscore ≤ 1.	40 (44.0)	126 (71.2)	26.78(14.40, 39.15) P<0.001

The endpoints for the histology evaluations are given in a separate table, since this endpoint included only part of the patient population (observed population with histology evaluation available).

Table 41: Exploratory efficacy endpoints – reported randomised strata with modified FAS, population with MMS 5-9 – Study APD334-302.

Endpoint	Study APD334-302		
	Placebo **N = 93** **n (%)**	**Etrasimod 2 mg** **N = 196** **n (%)**	**% Difference** **(2-sided p-value)[a]**
Histologic improvement (Geboes ≤ 3.1,)	28 (30.1)	99 (50.5)	19.84(8.47, 31.20) P<0.001
Histologic improvement (≥ 50% reduction in RHI or RHI ≤ 3 (Robarts Index))	32 (35.2)	104 (54.7)	18.82(7.00, 30.64) 0.002
Histologic improvement **(**≥ 1-point reduction from Baseline NHI (Nancy-Index))	43 (46.2)	105 (53.6)	7.54(-4.93, 20.00) 0.236
Histologic remission (Geboes Index score < 2.0) **,.**	18 (19.4)	55 (28.2)	8.18(-1.75, 18.12) P=0.106
Histologic remission (RHI score ≤ 3, with scores of 0 (zero) for both Geboes Grade 2B (lamina propria neutrophils) and Grade 3 (neutrophils in epithelium))	23 (25.3)	75 (39.5)	13.37(2.47, 24.26) P=0.016
Histologic remission (NHI ≤1)	23 (24.7)	75 (38.3)	13.10(2.42, 23.78) P=0.016

In this analysis, the deviating results with regard to the different histology scores appears remarkable, however, overall, the histology results seem to be in accordance with the overall results. The re-analysis with the different imputation methods for missing values have overall shown the robustness of the results.

Extraintestinal manifestations: There was no improvement in extraintestinal manifestations.

MMS "numerical evaluation": Subjects treated with etrasimod achieved clinically significant MMS change from Baseline at Week 12 compared with placebo (LS Mean difference: -1.05 [95% CI: -1.57, -0.53]; 2-sided p-value < 0.001). Similar results could be demonstrated for the RB and SF scores and these have shown robustness with regard to different imputation methods.

Subjects treated with etrasimod demonstrated significantly greater improvement in IBDQ total score (mean [SD] change from Baseline: etrasimod: 45.5 [40.03]; placebo: 30.4 [38.62]; 2-sided p-value < 0.001) compared with placebo. Overall, etrasimod treated subjects also showed significantly greater improvement in each of the four IBDQ subscores compared with placebo (2-sided p-value < 0.002). Other scales of health-related QoL showed either inconsistent results or were not reported in fully appropriate manner. The re-evaluations requested have confirmed overall inconsistency for the instruments other than IBDQ.

High-sensitivity CRP was reduced in both etrasimod and placebo groups and there was no significant difference between groups. LS mean difference: -1.226 (-5.095, 2.643); p=0.533.

Faecal Calprotectin: The baseline values was 2107.96 in the placebo, and 2544.06 in the active group (median 872.3 and 960.5). There was a final value measured at week 12 of 2034.81 for placebo, and 1567.33 for the active treatment group, the respective changes were – 160.6 and -261.47. The LS mean difference (95% CI) was -553.38 (-1868.75, 761,98), which was not significant (p=0.408).

The applicant conducted a few supplementary ad hoc analyses after excluding subjects who only failed oral 5-ASAs in prior treatment of UC and/or subjects with isolated proctitis also for APD334-302 study.

In contrast to study APD334-301, exclusion of subjects with both 5-ASA failure and/or isolated proctitis from analyses in study APD334-302, did partly change the conclusions for the key secondary endpoints for endoscopic improvement and mucosal healing at week 12 but not when only the single subgroups were excluded (which was demonstrated with additional evaluations). Results for symptomatic remission remained statistically significant. This finding could also partially be explained by the overall high placebo response rate, which was satisfactorily explained by the applicant (see above) The results are shown in the following table:

Table 42: Ad hoc supplementary analyses – FAS population MMS 4-9 Except Subjects who Only Failed Prior Oral 5-ASA and/or had Isolated Proctitis Based on Central Read - Study APD334-302

Study APD334-302				
		Placebo **N = 93** **n (%)**	**Etrasimod 2 mg** **N = 196** **n (%)**	**% Difference** **(2-sided p-value)**
Endoscopic improvement	Week 12	20 (21.5)	60 (30.6)	8.13 (-1.88, 18.13), p=0.1116
Symptomatic remission	Week 12	27 (29.0)	95 (48.5)	18.82 (7.35, 30.28), p=0.0013
Mucosal healing	Week 12	8 (8.6)	30 (15.3)	6.43 (-1.02, 13.87), p=0.0906

In additional supplementary analysis, etrasimod was superior to placebo also in achieving composite endpoint of endoscopic normalisation and histologic remission at week 12 in FAS MMS 5-9 (10.4% vs 4.5%, p=0.0298).

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 43: Summary of Efficacy results for Study APD-334-302

<table>
<tr><td colspan="4">Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, 12-Week Study to Assess the Efficacy and Safety of Etrasimod in Subjects with Moderately to Severely Active Ulcerative Colitis</td></tr>
<tr><td>Study identifier</td><td colspan="3">Study APD334-302
EudraCT number: 2018-003986-33</td></tr>
<tr><td>Design</td><td colspan="3">This was a multicentre, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of etrasimod 2 mg in subjects with moderately to severely active ulcerative colitis (UC). Eligible subjects were randomised in a 2:1 ratio to receive either etrasimod 2 mg once daily or matching placebo once daily for 12 weeks.
Entry into the study was based on confirmation of moderately to severely active UC defined by a modified Mayo score (MMS) of 4 to 9, which included endoscopic score (ES) ≥ 2 and rectal bleeding (RB) score ≥ 1. Subjects were required to have had an inadequate response to, loss of response to, or intolerance to at least 1 therapy for UC. The target subject population planned to include approximately 50% of subjects in each of the following categories:
1. Subjects who have had an inadequate response to, loss of response to, or intolerance to conventional therapy and were naïve to biologic or Janus kinase (JAK) inhibitor therapy
2. Subjects who have had an inadequate response to, loss of response to, or intolerance to a biologic or JAK inhibitor
Randomisation was stratified by (a) naïve to biologic or JAK inhibitor therapy at study entry (yes or no), (b) Baseline corticosteroid use (yes or no), and (c) Baseline disease activity (MMS: 4 to 6 or 7 to 9).
Study duration was 28 days for screening, 12-Week for treatment Period and 2 and 4-week Follow-up Periods. Scheduled visits occurred at Week 0/Day 1 and at Weeks 2, 4, 8, and 12. Primary and key secondary efficacy endpoints were assessed at Week 12. Safety assessments were performed at each study visit and at the discretion of the Investigator.
At the end of the 12-Week Induction Treatment Period, subjects had the option to enter an Open-Label Extension (OLE) Study APD334-303 provided they met eligibility criteria.
Subjects who did not participate in the OLE study had 2-Week and 4-Week Follow-Up visits after their last administration of study treatment. If the Early Termination (ET) visit was ≥ 2 weeks after the last administration of study treatment, the 2-Week Follow-Up visit was not required. If the ET visit was ≥ 4 weeks after the last administration of study treatment, the 4-Week Follow-Up visit was not required.</td></tr>
<tr><td></td><td colspan="2">Duration of main phase:
Duration of run-in phase:
Duration of extension phase:</td><td>12 weeks
Not applicable
Not applicable</td></tr>
<tr><td>Hypothesis</td><td colspan="3">Superiority</td></tr>
<tr><td>Treatments groups</td><td colspan="2">Etrasimod 2 mg</td><td>2 mg oral film-coated tablet, once daily
238 randomised</td></tr>
<tr><td></td><td colspan="2">Placebo</td><td>Mannitol oral film-coated tablet, once daily
116 randomised</td></tr>
<tr><td>Endpoints and definitions</td><td>Primary endpoint</td><td>The proportion of subjects achieving clinical remission at Week 12</td><td>Stool frequency (SF) subscore = 0 (or = 1 with a ≥ 1-point decrease from Baseline), RB subscore = 0, and ES ≤ 1 (excluding friability)</td></tr>
<tr><td></td><td>Key secondary endpoint</td><td>The proportion of subjects achieving endoscopic improvement at Week 12</td><td>ES of ≤ 1 (excluding friability)</td></tr>
</table>

	Key secondary endpoint	The proportion of subjects achieving symptomatic remission at Week 12	SF subscore = 0 (or = 1 with a ≥ 1-point decrease from Baseline) and RB subscore = 0
	Key secondary endpoint	The proportion of subjects with mucosal healing at Week 12	ES of ≤ 1 (excluding friability) with histologic remission measured by a Geboes Index score < 2.0

Database lock	Date: 17 February 2022		
Results and Analysis			
Analysis Description	**Primary Analysis – Clinical Remission**		
Analysis population and timepoint description	Full Analysis Set (FAS) and Actual Baseline MMS 5 to 9 at Week 12		
Descriptive statistics and estimate variability	Treatment group	Placebo	Etrasimod 2 mg
	Number of subjects, N	112	222
	Clinical remission responders [a], n (%)	17 (15.2)	55 (24.8)
Effect estimate per comparison	Primary endpoint	Comparison groups	Etrasimod 2 mg and Placebo
		% Difference from placebo	9.60
		Odds ratio (95% CI)[b]	1.90 (1.03, 3.52)
		% Difference (95% CI) [b]	9.69 (1.14, 18.23)
		2-sided p-value [b]	0.026
Notes	[a] Responders are defined as subjects who have SF subscore = 0 (or = 1 with a ≥ 1-point decrease from Baseline), rectal bleeding (RB) subscore = 0, and ES ≤ 1 (excluding friability). [b] Estimates are from a Cochran Mantel Haenszel (CMH) test, stratified by naïve to biologic/JAK inhibitor therapy at study entry (Y/N), Baseline corticosteroid use (Y/N), and Baseline disease activity (MMS: 4 to 6 or 7 to 9). Ratio is for etrasimod over placebo. Difference (%) is for etrasimod minus placebo and is based on estimated common risk difference using the Mantel-Haenszel weights. The 2-sided nominal p-value is to test the hypothesis of the risk difference being 0. Percentages are based on the number of subjects in the analysis set. Subjects missing an assessment at the specified analysis visit are considered nonresponders. The results of sensitivity and supplementary analyses support the primary analysis results, including a significantly greater proportion of subjects in the FAS (subjects with Baseline MMS 4 to 9) who achieved clinical remission at Week 12 with etrasimod compared with placebo. Source: Study APD334-302 Clinical Study Report (CSR) Table 11		

Analysis Description	**Key Secondary Analysis – Endoscopic Improvement**		
Analysis population and timepoint description	Full Analysis Set and Actual Baseline MMS 5 to 9 at Week 12		
Descriptive statistics and estimate variability	Treatment group	Placebo	Etrasimod 2 mg
	Number of subjects	112	222
	Endoscopic improvement responders [a], n (%)	21 (18.8)	68 (30.6)
Effect estimate per comparison	Key secondary endpoint	Comparison groups	Etrasimod 2 mg and Placebo
		% Difference from placebo	11.88
		Odds ratio (95% CI)[b]	2.03 (1.14, 3.60)

		% Difference (95% CI) [b]	12.11 (3.00, 21.23)
		2-sided p-value [b]	0.009
Notes	[a] Responders are defined as subjects with an ES subscore ≤ 1 (excluding friability). [b] Estimates are from a CMH test, stratified by naïve to biologic/JAK inhibitor therapy at study entry (Y/N), Baseline corticosteroid use (Y/N), and Baseline disease activity (MMS: 4 to 6 or 7 to 9). Ratio is for etrasimod over placebo. Difference (%) is for etrasimod minus placebo and is based on estimated common risk difference using the Mantel-Haenszel weights. The 2-sided p-value is to test the hypothesis of the risk difference being 0. Percentages are based on the number of subjects in the analysis set. Subjects missing an assessment at the specified analysis visit are considered nonresponders. Only subjects with a Baseline MMS score between 5 and 9 are included. The results of sensitivity and supplementary analyses support the secondary analysis results, including a significantly greater proportion of subjects in the FAS (subjects with Baseline MMS 4 to 9) who achieved endoscopic improvement at Week 12 with etrasimod compared with placebo. Source: Study APD334-302 CSR Table 12		
Analysis Description	**Key Secondary Analysis – Symptomatic Remission**		
Analysis population and timepoint description	Full Analysis Set and Actual Baseline MMS 5 to 9 at Week 12		
Descriptive statistics and estimate variability	Treatment group	Placebo	Etrasimod 2 mg
	Number of subjects	112	222
	Symptomatic remission responders [a], n (%)	33 (29.5)	104 (46.8)
Effect estimate per comparison	Key secondary endpoint	Comparison groups	Etrasimod 2 mg and Placebo
		% Difference from placebo	17.38
		Odds ratio (95% CI) [b]	2.13 (1.31, 3.46)
		% Difference (95% CI) [b]	17.48 (6.81, 28.15)
		2-sided p-value [b]	0.001
Notes	[a] Responders are defined as subjects with a SF subscore = 0 (or = 1 with a ≥ 1-point decrease from baseline) and RB subscore = 0 [b] Estimates are from a CMH test, stratified by naïve to biologic/JAK inhibitor therapy at study entry (Y/N), Baseline corticosteroid use (Y/N), and Baseline disease activity (MMS: 4 to 6 or 7 to 9). Ratio is for etrasimod over placebo. Difference (%) is for etrasimod minus placebo and is based on estimated common risk difference using the Mantel-Haenszel weights. The 2-sided p-value is to test the hypothesis of the risk difference being 0. Percentages are based on the number of subjects in the analysis set. Subjects missing an assessment at the specified analysis visit are considered nonresponders. Only subjects with a Baseline MMS score between 5 and 9 are included. The results of sensitivity and supplementary analyses support the secondary analysis results, including a significantly greater proportion of subjects in the FAS (subjects with Baseline MMS 4 to 9) who achieved symptomatic remission at Week 12 with etrasimod compared with placebo. Source: Study APD334-302 CSR Table 13		
Analysis Description	**Key Secondary Analysis – Mucosal Healing**		
Analysis population and timepoint description	Full Analysis Set and Actual Baseline MMS 5 to 9 at Week 12		
Descriptive statistics and estimate variability	Treatment group	Placebo	Etrasimod 2 mg
	Number of subjects	112	222
	Mucosal healing responders [a], n (%)	10 (8.9)	36 (16.2)
Effect estimate per comparison	Key secondary endpoint	Comparison groups	Etrasimod 2 mg and Placebo
		% Difference from placebo	7.29
		Odds ratio (95% CI) [b]	2.09 (0.97, 4.50)

		% Difference (95% CI) [b]	7.44 (0.50, 14.39)
		2-sided p-value [b]	0.036
Notes	[a] Responders are defined as subjects who have an ES ≤ 1 (excluding friability) with histologic remission measured by a Geboes Index score < 2.0 [b] Estimates are from a CMH test, stratified by naïve to biologic/JAK inhibitor therapy at study entry (Y/N), Baseline corticosteroid use (Y/N), and Baseline disease activity (MMS: 4 to 6 or 7 to 9). Ratio is for etrasimod over placebo. Difference (%) is for etrasimod minus placebo and is based on estimated common risk difference using the Mantel-Haenszel weights. The 2-sided p-value is to test the hypothesis of the risk difference being 0. Percentages are based on the number of subjects in the analysis set. Subjects missing an assessment at the specified analysis visit are considered nonresponders. Only subjects with a Baseline MMS score between 5 and 9 are included. The results of sensitivity and supplementary analyses support the secondary analysis results, including a significantly greater proportion of subjects in the FAS (subjects with Baseline MMS 4 to 9) who achieved mucosal healing at Week 12 with etrasimod compared with placebo. Source: Study APD334-302 CSR Table 14		

Table 44: Summary of Efficacy results for Study APD-334-301

Title: A Phase 3, Randomized, Double Blind, Placebo Controlled, 52 Week Study to Assess the Efficacy and Safety of Etrasimod in Subjects with Moderately to Severely Active Ulcerative Colitis	
Study identifier	Study APD334-301 EudraCT number: 2018-003985-15
Design	Study *Design: This was a multicentre, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of etrasimod 2 mg in subjects with moderately to severely active ulcerative colitis (UC). Eligible subjects were randomised in a 2:1 ratio to receive either etrasimod 2 mg once daily or matching placebo once daily for up to 52 weeks, which included 12-Week and 40-Week Treatment Periods.* Entry *into the study was based on confirmation of moderately to severely active UC defined by a modified Mayo score (MMS) of 4 to 9, which included endoscopic score (ES) ≥ 2 and rectal bleeding (RB) score ≥ 1.* *Subjects were required to have had an inadequate response to, loss of response to, or intolerance to at least 1 therapy for UC. The target subject population planned to include approximately 50% of subjects in each of the following categories:* *Subjects who have had an inadequate response to, loss of response to, or intolerance to conventional therapy and were naïve to biologic or Janus kinase (JAK) inhibitor therapy* *Subjects who have had an inadequate response to, loss of response to, or intolerance to a biologic or JAK inhibitor* *Randomisation was stratified by (a) naïve to biologic or JAK inhibitor therapy at study entry (yes or no), (b) Baseline corticosteroid use (yes or no), and (c) Baseline disease activity (MMS: 4 to 6 or 7 to 9).* *Scheduled visits occurred at Week 0/Day 1 and at Weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, and 52. Primary and key secondary efficacy endpoints were assessed at Weeks 12 and 52. Safety assessments were performed at each study visit and at the discretion of the Investigator.* *Subjects who experienced disease worsening following the completion of the Week 12 Visit, or who experienced disease worsening during the 40 Week Treatment Period, or who completed all study procedures at Week 52, had the option to enter Open-Label Extension (OLE) Study APD334-303 provided they met eligibility criteria.* *Subjects who did not participate in the OLE study had 2-Week and 4-Week Follow-Up Visits after their last administration of study treatment. If the early*

	termination (ET) visit was ≥ 2 weeks after the last dose of study treatment, the 2-Week Follow-Up Visit was not required. If the ET visit was ≥ 4 weeks after the last administration of study treatment, the 4-Week Follow-Up Visit was not required unless the absolute lymphocyte count (ALC) was not within normal limits.		
	Duration of main phase:		52 weeks
	Duration of run-in phase:		Not applicable
	Duration of extension phase:		Not applicable
Hypothesis	Superiority		
Treatments groups	Etrasimod 2 mg		2 mg oral film-coated tablet, once daily; 289 randomised
	Placebo		Mannitol oral film-coated tablet, once daily; 144 randomised
Endpoints and definitions	Co-primary endpoint	The proportion of subjects achieving clinical remission at Week 12	Stool frequency (SF) subscore = 0 (or = 1 with a ≥ 1-point decrease from Baseline), RB subscore = 0, and ES ≤ 1 (excluding friability)
	Co-primary endpoint	The proportion of subjects achieving clinical remission at Week 52	SF subscore = 0 (or = 1 with a ≥ 1-point decrease from Baseline), RB subscore = 0, and ES ≤ 1 (excluding friability)
	Key secondary endpoint	The proportion of subjects achieving endoscopic improvement at Week 12	ES of ≤ 1 (excluding friability)
	Key secondary endpoint	The proportion of subjects achieving endoscopic improvement at Week 52	ES of ≤ 1 (excluding friability)
	Key secondary endpoint	The proportion of subjects achieving symptomatic remission at Week 12	SF subscore = 0 (or = 1 with a ≥ 1-point decrease from Baseline) and RB subscore = 0
	Key Secondary endpoint	The proportion of subjects achieving symptomatic remission at Week 52	SF subscore = 0 (or = 1 with a ≥ 1-point decrease from Baseline) and RB subscore = 0
	Key Secondary endpoint	The proportion of subjects achieving corticosteroid-free clinical remission at Week 52	Clinical remission at Week 52 and who had not been receiving corticosteroids for ≥ 12 weeks prior to Week 52

	Key Secondary endpoint	The proportion of subjects achieving sustained clinical remission	Clinical remission at both Weeks 12 and 52
	Key Secondary endpoint	The proportion of subjects with mucosal healing at Week 12	ES of ≤ 1 (excluding friability) with histologic remission measured by a Geboes Index score < 2.0
	Key secondary endpoint	The proportion of subjects with mucosal healing at Week 52	ES of ≤ 1 (excluding friability) with histologic remission measured by a Geboes Index score < 2.0
	Ad hoc endpoint	The proportion of subjects achieving corticosteroid-free endoscopic improvement at Week 52	ES ≤1 (excluding friability) and corticosteroid-free for ≥ 12 weeks immediately prior to Week 52
	Ad hoc endpoint	The proportion of subjects achieving corticosteroid-free symptomatic remission at Week 52	SF subscore = 0 (or = 1 with a ≥ 1-point decrease from Baseline), RB subscore = 0, and corticosteroid-free for ≥ 12 weeks immediately prior to Week 52

Database lock	Date: 10 March 2022		
Results and Analysis			
Analysis Description	**Primary Analysis – Clinical Remission**		
Analysis population and timepoint description	Full Analysis Set (FAS)and Actual Baseline MMS 5 to 9 at Week 12		
Descriptive statistics and estimate variability	Treatment group	Placebo	Etrasimod 2 mg
	Number of subjects, N	135	274
	Clinical remission responders [a], n (%)	10 (7.4)	74 (27.0)
Effect estimate per comparison	Primary endpoint	Comparison groups	Etrasimod 2 mg and Placebo
		% Difference from placebo	19.60
		Odds ratio (95% CI) [b]	4.68 (2.32, 9.44)
		% Difference (95% CI) [b]	19.75 (12.88, 26.63)
		2-sided p-value [b]	< 0.001
Analysis population and timepoint description	Full Analysis Set (FAS)and Actual Baseline MMS 5 to 9 at Week 52		
Descriptive statistics and estimate variability	Treatment group	Placebo	Etrasimod 2 mg
	Number of subjects, N	135	274

	Clinical remission responders [a], n (%)	9 (6.7)	88 (32.1)
Effect estimate per comparison	Primary endpoint	Comparison groups	Etrasimod 2 mg and Placebo
		% Difference from placebo	25.45
		Odds ratio (95% CI)[b]	6.54 (3.18, 13.44)
		% Difference (95% CI) [b]	25.39 (18.42, 32.36)
		2-sided p-value [b]	< 0.001
Notes	[a] Responders are defined as subjects who have SF subscore = 0 (or = 1 with a ≥ 1-point decrease from Baseline), RB subscore = 0, and ES ≤ 1 (excluding friability). [b] Estimates are from a Cochran Mantel Haenszel (CMH) test, stratified by naïve to biologic/JAK inhibitor therapy at study entry (Y/N), Baseline corticosteroid use (Y/N), and Baseline disease activity (MMS: 4 to 6 or 7 to 9). Ratio is for etrasimod over placebo. Difference (%) is for etrasimod minus placebo and is based on estimated common risk difference using the Mantel-Haenszel weights. The 2-sided p-value is to test the hypothesis of the risk difference being 0. Percentages are based on the number of subjects in the analysis set. Subjects missing an assessment at the specified analysis visit are considered nonresponders. The results of sensitivity and supplementary analyses support the primary analysis results, including a significantly greater proportion of subjects in the FAS (subjects with Baseline MMS 4 to 9) who achieved clinical remission at Week 12 and Week 52 with etrasimod compared with placebo. Source: Study APD334-301 Clinical Study Report (CSR) Table 11		
Analysis Description	**Key Secondary Analysis – Endoscopic Improvement**		
Analysis population and timepoint description	Full Analysis Set (FAS) and Actual Baseline MMS 5 to 9 at Week 12		
Descriptive statistics and estimate variability	Treatment group	Placebo	Etrasimod 2 mg
	Number of subjects	135	274
	Endoscopic improvement responders [a], n (%)	19 (14.1)	96 (35.0)
Effect estimate per comparison	Key secondary endpoint	Comparison groups	Etrasimod 2 mg and Placebo
		% Difference from placebo	20.96
		Odds ratio (95% CI)[b]	3.33 (1.93, 5.76)
		% Difference (95% CI) [b]	21.18 (13.03, 29.32)
		2-sided p-value [b]	< 0.001
Analysis population and timepoint description	Full Analysis Set (FAS) and Actual Baseline MMS 5 to 9 at Week 52		
Descriptive statistics and estimate variability	Treatment group	Placebo	Etrasimod 2 mg
	Number of subjects	135	274
	Endoscopic improvement responders [a], n (%)	14 (10.4)	102 (37.2)
Effect estimate per comparison	Key secondary endpoint	Comparison groups	Etrasimod 2 mg and Placebo
		% Difference from placebo	26.86
		Odds ratio (95% CI)[b]	5.10 (2.77, 9.37)
		% Difference (95% CI) [b]	26.69 (18.99, 34.39)
		2-sided p-value [b]	< 0.001
Notes	[a] Responders are defined as subjects with an ES subscore ≤ 1 (excluding friability). [b] Estimates are from a CMH test, stratified by naïve to biologic/JAK inhibitor therapy at study entry (Y/N), Baseline corticosteroid use (Y/N), and Baseline disease activity (MMS: 4 to 6 or 7 to 9). Ratio is for etrasimod over placebo. Difference (%) is for		

	etrasimod minus placebo and is based on estimated common risk difference using the Mantel-Haenszel weights. The 2-sided p-value is to test the hypothesis of the risk difference being 0. Percentages are based on the number of subjects in the analysis set. Subjects missing an assessment at the specified analysis visit are considered nonresponders. Only subjects with a Baseline MMS score between 5 and 9 are included. The results of sensitivity and supplementary analyses support the primary analysis results, including a significantly greater proportion of subjects in the FAS (subjects with Baseline MMS 4 to 9) who achieved clinical remission at Week 12 and Week 52 with etrasimod compared with placebo. Source: Study APD334-301 CSR Table 12		
Analysis description	**Key Secondary Analysis – Symptomatic Remission**		
Analysis population and timepoint description	Full Analysis Set (FAS) and Actual Baseline MMS 5 to 9 at Week 12		
Descriptive statistics and estimate variability	Treatment group	Placebo	Etrasimod 2 mg
	Number of subjects	135	274
	Symptomatic remission responders [a], n (%)	29 (21.5)	126 (46.0)
Effect estimate per comparison	Key secondary endpoint	Comparison groups	Etrasimod 2 mg and Placebo
		% Difference from placebo	24.50
		Odds ratio (95% CI) [b]	3.14 (1.95, 5.06)
		% Difference (95% CI) [b]	24.55 (15.46, 33.63)
		2-sided p-value [b]	< 0.001
Analysis population and timepoint description	Full Analysis Set (FAS) and Actual Baseline MMS 5 to 9 at Week 52		
Descriptive statistics and estimate variability	Treatment group	Placebo	Etrasimod 2 mg
	Number of subjects	135	274
	Symptomatic remission responders [a], n (%)	25 (18.5)	119 (43.4)
Effect estimate per comparison	Key secondary endpoint	Comparison groups	Etrasimod 2 mg and Placebo
		% Difference from placebo	24.91
		Odds ratio (95% CI)[b]	3.46 (2.09, 5.72)
		% Difference (95% CI) [b]	24.89 (16.17, 33.60)
		2-sided p-value [b]	< 0.001
Notes	[a] Responders are defined as subjects with a SF subscore = 0 (or = 1 with a ≥ 1-point decrease from Baseline) and RB subscore = 0. [b] Estimates are from a CMH test, stratified by naïve to biologic/JAK inhibitor therapy at study entry (Y/N), Baseline corticosteroid use (Y/N), and Baseline disease activity (MMS: 4 to 6 or 7 to 9). Ratio is for etrasimod over placebo. Difference (%) is for etrasimod minus placebo and is based on estimated common risk difference using the Mantel-Haenszel weights. The 2-sided p-value is to test the hypothesis of the risk difference being 0. Percentages are based on the number of subjects in the analysis set. Subjects missing an assessment at the specified analysis visit are considered nonresponders. Only subjects with a Baseline MMS score between 5 and 9 are included. The results of sensitivity and supplementary analyses support the primary analysis results, including a significantly greater proportion of subjects in the FAS (subjects with Baseline MMS 4 to 9) who achieved symptomatic remission at Week 12 and Week 52 with etrasimod compared with placebo. Source: Study APD334-301 CSR Table 13		

Analysis description	**Key Secondary Analysis – Corticosteroid-free Clinical Remission**		
Analysis population and timepoint description	Full Analysis Set (FAS) and Actual Baseline MMS 5 to 9 Week 52		
Descriptive statistics and estimate variability	Treatment group	Placebo	Etrasimod 2 mg
	Number of subjects	135	274
	Corticosteroid-free clinical remission responders [a], n (%)	9 (6.7)	88 (32.1)
Effect estimate per comparison	Key secondary endpoint	Comparison groups	Etrasimod 2 mg and Placebo
		% Difference from placebo	25.45
		Odds ratio (95% CI) [b]	6.54 (3.18, 13.44)
		% Difference (95% CI) [b]	25.39 (18.42, 32.36)
		2-sided p-value [b]	< 0.001
Notes	[a] Responders are defined as subjects with a SF subscore = 0 (or = 1 with a ≥ 1-point decrease from Baseline) and RB subscore = 0, ES ≤ 1 (excluding friability), and have not received corticosteroids for ≥ 12 weeks in the 40-Week Treatment Period. b Estimates are from a CMH test, stratified by naïve to biologic or JAK inhibitor therapy at study entry (Yes or No), Baseline corticosteroid use (Yes or No), and Baseline disease activity (MMS: 4 to 6 or 7 to 9). Ratio is for etrasimod over placebo. Difference (%) is for etrasimod minus placebo and is based on estimated common risk difference using the Mantel-Haenszel weights. The 2-sided p-value is to test the hypothesis of the risk difference being 0. Percentages are based on the number of subjects in the analysis set. Subjects missing an assessment at the specified analysis visit are considered nonresponders. Only subjects with a Baseline MMS score between 5 and 9 are included. The results of supplementary analyses support the primary analysis results, including a significantly greater proportion of subjects in the FAS (subjects with Baseline MMS 4 to 9) who achieved corticosteroid-free clinical remission at Week 52 with etrasimod compared with placebo. Source: Study APD334-301 CSR Table 15		
Analysis description	**Key Secondary Analysis – Sustained Clinical Remission**		
Analysis population and timepoint description	Full Analysis Set (FAS) and Actual Baseline MMS 5 to 9 at Week 12 and Week 52		
Descriptive statistics and estimate variability	Treatment group	Placebo	Etrasimod 2 mg
	Number of subjects	135	274
	Sustained clinical remission responders [a], n (%)	3 (2.2)	49 (17.9)
Effect estimate per comparison	Key secondary endpoint	Comparison groups	Etrasimod 2 mg and Placebo
		% Difference from placebo	15.66
		Odds ratio (95% CI)[b]	9.81 (2.98, 32.36)
		% Difference (95% CI) [b]	15.84 (10.66, 21.03)
		2-sided p-value [b]	< 0.001

Notes	[a] Responders are defined as subjects with a SF subscore = 0 (or = 1 with a ≥ 1-point decrease from Baseline), RB subscore = 0, and ES ≤ 1 (excluding friability) at both Week 12 and Week 52. [b] Estimates are from a CMH test, stratified by naïve to biologic or JAK inhibitor therapy at study entry (Yes or No), Baseline corticosteroid use (Yes or No), and Baseline disease activity (MMS: 4 to 6 or 7 to 9). Ratio is for etrasimod over placebo. Difference (%) is for etrasimod minus placebo and is based on estimated common risk difference using the Mantel-Haenszel weights. The 2-sided p-value is to test the hypothesis of the risk difference being 0. Percentages are based on the number of subjects in the analysis set. Subjects missing an assessment at the specified analysis visit are considered nonresponders. Only subjects with a Baseline MMS score between 5 and 9 are included. The results of supplementary analyses support the primary analysis results, including a significantly greater proportion of subjects in the FAS (subjects with Baseline MMS 4 to 9) who achieved sustained clinical remission at Week 12 and Week 52 with etrasimod compared with placebo. Source: Study APD334-301 CSR Table 16		
Analysis description	**Key Secondary Analysis – Mucosal Healing**		
Analysis population and timepoint description	Full Analysis Set (FAS) and Actual Baseline MMS 5 to 9 at Week 12		
Descriptive statistics and estimate variability	Treatment group	Placebo	Etrasimod 2 mg
	Number of subjects	135	274
	Mucosal healing responders [a], n (%)	6 (4.4)	58 (21.2)
Effect estimate per comparison	Key secondary endpoint	Comparison groups	Etrasimod 2 mg and Placebo
		% Difference from placebo	16.72
		Odds ratio (95% CI) [b]	5.38 (2.32, 12.45)
		% Difference (95% CI) [b]	16.88 (10.78, 22.98)
		2-sided p-value [b]	< 0.001
Analysis population and timepoint description	Strata Full Analysis Set (FAS) and Actual Baseline MMS 5 to 9 at Week 52		
Descriptive statistics and estimate variability	Treatment group	Placebo	Etrasimod 2 mg
	Number of subjects	135	274
	Mucosal healing responders [a], n (%)	11 (8.1)	73 (26.6)
Effect estimate per comparison	Key secondary endpoint	Comparison groups	Etrasimod 2 mg and Placebo
		% Difference from placebo	18.49
		Odds ratio (95% CI)[b]	4.05 (2.07, 7.92)
		% Difference (95% CI) [b]	18.39 (11.39, 25.39)
		2-sided p-value [b]	< 0.001

Notes	[a] Responders are defined as subjects who have an ES ≤ 1 (excluding friability) with histologic remission measured by a Geboes Index score < 2.0. [b] Estimates are from a CMH test, stratified by naïve to biologic/JAK inhibitor therapy at study entry (Y/N), Baseline corticosteroid use (Y/N), and Baseline disease activity (MMS: 4 to 6 or 7 to 9). Ratio is for etrasimod over placebo. Difference (%) is for etrasimod minus placebo and is based on estimated common risk difference using the Mantel-Haenszel weights. The 2-sided p-value is to test the hypothesis of the risk difference being 0. Percentages are based on the number of subjects in the analysis set. Subjects missing an assessment at the specified analysis visit are considered nonresponders. Only subjects with a Baseline MMS score between 5 and 9 are included. The results of sensitivity and supplementary analyses support the primary analysis results, including a significantly greater proportion of subjects in the FAS (subjects with Baseline MMS 4 to 9) who achieved mucosal healing at Week 12 and Week 52 with etrasimod compared with placebo. Source: Study APD334-301 CSR Table 14		
Analysis description	**Ad Hoc Analysis – Corticosteroid-Free Endoscopic Improvement**		
Analysis population and timepoint description	Full Analysis Set (FAS) and Actual Baseline MMS 5 to 9 at Week 52		
Descriptive statistics and estimate variability	Treatment group	Placebo	Etrasimod 2 mg
	Number of subjects	135	274
	Clinical response responders [a], n (%)	14 (10.4)	101 (36.9)
Effect estimate per comparison	Other secondary endpoint	Comparison groups	Etrasimod 2 mg and Placebo
		% Difference from placebo	26.49
		Odds ratio (95% CI)[b]	5.01 (2.73, 9.21)
		% Difference (95% CI) [b]	26.35 (18.65, 34.04)
		2-sided p-value [b]	< 0.001
Notes	[a] Responders are defined as subjects with an ES ≤ 1 (excluding friability) and corticosteroid-free for ≥ 12 weeks immediately prior to Week 52 [b] Estimates are from a CMH test, stratified by naïve to biologic/JAK. inhibitor therapy at study entry (Y/N), Baseline corticosteroid use (Y/N), and Baseline disease activity (MMS: 4 to 6 or 7 to 9). Ratio is for etrasimod over placebo. Difference (%) is for etrasimod minus placebo and is based on estimated common risk difference using the Mantel-Haenszel weights. The 2-sided p-value is to test the hypothesis of the risk difference being 0. Percentages are based on the number of subjects in the analysis set. Subjects missing an assessment at the specified analysis visit are considered nonresponders. Only subjects with a Baseline MMS score between 5 and 9 are included. Source: Study APD334-301 CSR Table 14.2.2.21		
Analysis description	**Ad Hoc Analysis - Corticosteroid–Free Symptomatic Remission**		
Analysis population and timepoint description	Full Analysis Set (FAS) and Actual Baseline MMS 5 to 9 at Week 52		
Descriptive statistics and estimate variability	Treatment group	Placebo	Etrasimod 2 mg
	Number of subjects	135	274
	Clinical response responders [a], n (%)	25 (18.5)	119 (43.4)

2.6.5.3. Clinical studies in special populations

No studies in special populations are presented by the applicant.

However, the following facts need to be noted:

- Adolescents: While the applicant claims the treatment of adolescents, and the two pivotal studies have been trying to recruit patients from the age of 16 and above, the number of patients aged below 18 at the time of inclusion was extremely low, with a total of 3 patients (of which 1 was in the etrasimod, and 2 in the placebo groups).

Therefore, granting the indication in adolescents from 16 years of age is based on extrapolation from adult patients.

Although some differences in disease severity between children and adults exist, the pathogenesis of UC and disease course can be considered similar enough to allow extrapolation of efficacy from adults to older adolescents based on similar exposure of etrasimod.

According to the Pop PK analysis, no significant differences in etrasimod exposure are expected between older adolescents and adults with UC. Limited additional paediatric data (n=2) from the ongoing PIP study showed etrasimod steady-state exposure within the adult range.

Due to limited data in patients 16 to <18 years, the applicant provided additional analyses of efficacy, safety, PKPD and exposure-response, comparing young adults (≤25 years, n=101) to older adults (>25 years, n=642). Overall, responder rates at Week 12 appear generally similar between young adults and older adults, except for the endoscopic improvement that was less in the younger adults group. 52 week data come only from study APD334-301 with a high discontinuation rate of young adults (only 17 subjects ≤25 years completed the study). Thus, it is difficult to make an efficacy comparison at Week 52. Safety profile in general appears similar between the two groups. PK/PD modelling and exposure-response analyses did not suggest any clinically meaningful difference between younger and older adults.

- In a similar way, and as reported above, the number of patients above the age of 65 and especially above the age of 75 was also very low. In study -301, 27 patients were aged 65 or older, while only 3 were aged 75 years or older. In study -302, 18 patients were aged 65 or older, but none was aged 75 or older. The total number of elderly patients therefore sums up to 45 only. For the elderly population further additional analyses were presented and did not leave a concern with regard to efficacy. An adequate warning statement on the limited number of patients treated in the clinical trials is included in the PI.

At request, the applicant has presented the results of a study that has been completed during the assessment period. This study, is in principle a long-term study similar to study 301, included the Japanese patients from study 302 only. The patients were treated for 40 additional weeks with their original treatment assignment. In study 302, 48 Japanese patients were randomised, and of these 42 completed week 12. Completion of study was achieved with 4 (28.6%) in the placebo, and 18 (64.3%) patients in the active treatment group.

The selected main results are shown in the following table:

Table 45: Primary and secondary endpoints study 308 (week 52):

Endpoint	Study APD334-308		
	Placebo N = 14 n (%)	**Etrasimod 2 mg N = 28 n (%)**	**% Difference (2-sided p-value)[a]**
Clinical remission	1 (7.1%)	7 (25.0%)	17.86 (-3.10, 38.82) P<0.233
Endoscopic improvement	1 (7.1)	10 (35.7)	28.57 (6.28; 50.86) P=0.067
Symptomatic remission	1 (7.1)	11 (39.3)	32.14 (9.58, 54.71) P=0.036
Mucosal healing	1 (7.1)	8 (28.6)	21.43 (-0.07, 42.92 P=0.230

The results of the long-term extension for the Japanese patients were largely in accordance with the results of study 301 with effect sizes being partly greater than observed in study 301. However, overall statistical significance was not achieved.

Upon request, the applicant has also presented interim efficacy evaluation of the open-label, long-term extension study APD334-303. The results presented were generally supportive of the results of the controlled trials.

2.6.5.4. Analysis performed across trials (pooled analyses and meta-analysis)

A pooled analyses of the results is possible only for the 12 week time-point. The primary endpoint, and the endpoints representing (almost) the requirements of the CHMP UC guideline are presented in the following:

Pooled results for primary and selected secondary endpoints:

Table 46: Clinical Remission at Week 12 (PAS with Actual Baseline MMS 5 to 9) – pooled data

Timepoint Summary	Study APD334-301		Study APD334-302		Pooled	
	Placebo (N = 135)	**Etrasimod 2 mg (N = 274)**	**Placebo (N = 112)**	**Etrasimod 2 mg (N = 222)**	**Placebo (N = 247)**	**Etrasimod 2 mg (N = 496)**
Week 12						
Responders[a], n (%)	10 (7.4)	74 (27.0)	17 (15.2)	55 (24.8)	27 (10.9)	129 (26.0)
% Difference from Placebo		19.60		9.60		15.08
Odds Ratio (95% CI)[b]		4.68 (2.32, 9.44)		1.90 (1.03, 3.52)		2.95 (1.87, 4.65)
% Difference (95% CI) [b]		19.75 (12.88, 26.63)		9.69 (1.14, 18.23)		15.20 (9.77, 20.63)
2-sided p-value [b]		<0.001		0.026		<0.001

a Responders are defined as subjects who have SF subscore = 0 (or = 1 with a ≥ 1 point decrease from Baseline), RB subscore = 0, and ES ≤ 1 (excluding friability).

b Estimates are from a CMH test, stratified by study (for Pooled analysis only), naïve to biologic/JAK inhibitor therapy at study entry (Y/N), Baseline corticosteroid use (Y/N), and Baseline disease activity (MMS: 4 to 6 or 7 to 9). Ratio is for etrasimod over placebo. Difference (%) is for etrasimod minus placebo and is based on estimated common risk difference using the Mantel-Haenszel weights. Unadjusted p-value is reported. The 2-sided p-value is to test the hypothesis of the risk difference being 0.
Note: Only subjects with a Baseline MMS score between 5 and 9 are included.
Percentages are based on the number of subjects in the analysis set.
Subjects missing an assessment at the specified analysis visit are considered nonresponders.
Source: ISE Table 14.2.1.1

Table 47: Symptomatic Remission at Week 12 – (PAS with Actual Baseline MMS 5 to 9)

Timepoint Summary	Study APD334-301		Study APD334-302		Pooled	
	Placebo (N = 135)	Etrasimod 2 mg (N = 274)	Placebo (N = 112)	Etrasimod 2 mg (N = 222)	Placebo (N = 247)	Etrasimod 2 mg (N =4 96)
Week 12						
Responders[a], n(%)	29 (21.5)	126 (46.0)	33 (29.5)	104 (46.8)	62 (25.1)	230 (46.4)
% Difference from Placebo		24.50		17.38		21.27
Odds Ratio (95% CI)[b]		3.14 (1.95, 5.06)		2.13 (1.31, 3.46)		2.61 (1.86, 3.66)
% Difference (95% CI) [b]		24.55 (15.46, 33.63)		17.48 (6.81, 28.15)		21.35 (14.41, 28.30)
2-sided p-value[b]		<0.001		0.001		<0.001

a Responders are defined as subjects who have SF subscore = 0 (or = 1 with a ≥ 1 point decrease from Baseline) and RB subscore = 0.
b Estimates are from a CMH test, stratified by study (for Pooled analyses only), naïve to biologic/JAK inhibitor therapy at study entry (Y/N), Baseline corticosteroid use (Y/N), and Baseline disease activity (MMS: 4 to 6 or 7 to 9). Ratio is for etrasimod over placebo. Difference (%) is for etrasimod minus placebo and is based on estimated common risk difference using the Mantel-Haenszel weights. Unadjusted p-value is reported. The 2-sided p-value is to test the hypothesis of the risk difference being 0.
Note: Only subjects with a Baseline MMS score between 5 and 9 are included.
Percentages are based on the number of subjects in the analysis set.
Subjects missing an assessment at the specified analysis visit are considered nonresponders.
Source: ISE Table 14.2.2.2

Table 48: Mucosal Healing at Week 12 – (FAS with Actual Baseline MMS 5 to 9)

Timepoint Summary	Study APD334-301		Study APD334-302		Pooled	
	Placebo (N = 135)	Etrasimod 2 mg (N = 274)	Placebo (N = 112)	Etrasimod 2 mg (N = 222)	Placebo (N = 247)	Etrasimod 2 mg (N = 496)
Week 12						
Responders[a], n(%)	6 (4.4)	58 (21.2)	10 (8.9)	36 (16.2)	16 (6.5)	94 (19.0)
% Difference from Placebo		16.72		7.29		12.47
Odds Ratio (95% CI)[b]		5.38 (2.32, 12.45)		2.09 (0.97, 4.50)		3.43 (1.97, 5.98)
% Difference (95% CI) [b]		16.88 (10.78, 22.98)		7.44 (0.50, 14.39)		12.61 (8.00, 17.23)

Timepoint Summary	Study APD334-301		Study APD334-302		Pooled	
	Placebo (N = 135)	Etrasimod 2 mg (N = 274)	Placebo (N = 112)	Etrasimod 2 mg (N = 222)	Placebo (N = 247)	Etrasimod 2 mg (N = 496)
2-sided p-value[b]		<0.001		0.036		<0.001

[a] Responders are defined as subjects who have an ES ≤ 1 (excluding friability) with histologic remission measured by a Geboes Index score < 2.0.
[b] Estimates are from a CMH test, stratified by study (for Pooled analyses only), naïve to biologic/JAK inhibitor therapy at study entry (Y/N), Baseline corticosteroid use (Y/N), and Baseline disease activity (MMS: 4 to 6 or 7 to 9). Ratio is for etrasimod over placebo. Difference (%) is for etrasimod minus placebo and is based on estimated common risk difference using the Mantel-Haenszel weights. Unadjusted p-value is reported. The 2-sided p-value is to test the hypothesis of the risk difference being 0.
Note:Only subjects with a Baseline MMS score between 5 and 9 are included.
Percentages are based on the number of subjects in the analysis set.
Subjects missing an assessment at the specified analysis visit are considered nonresponders.
Source: ISE Table 14.2.2.3

Pooled analysis for subgroups were also presented by the applicant, however, only in selected endpoints. Upon request, these have been completed with a full set of potentially relevant subgroups. For clinical remission, differences were seen between male and female patients in the single studies, which, however, levelled out in the pooled analysis, since the differences were in the opposite direction. Analyses were also presented for age (cut-off at median age), and region. The latter showed that the results tended to be better in the Eastern Europe region, while Western Europe and North America did not show statistical significance, and the treatment effect was somewhat reduced, as compared to Eastern Europe. Similarly, missed statistical significance and reduced magnitude of effects were also seen in patients with baseline corticosteroid use (as compared to those without). In patients with prior biologic/JAP inhibitor use also a somewhat reduced effect was seen (risk difference 17.2 vs. 10.8), however, statistical significance was seen in both subgroups.

The efficacy results demonstrated in the subgroup of patients with isolated proctitis are considered valuable because those patients are usually excluded from UC pivotal trials, and at least a trend of efficacy could be established. Differences detected for efficacy results presented in ISE and in the CSRs have been sufficiently explained by the applicant.

Isolated proctitis only patients have also been re-evaluated sufficiently and results were overall in accordance.

2.6.5.5. Supportive study(ies)

Study APD334-005 is presented as supportive evidence. The study was titled "An Extension Study of APD334-003 in Patients with Moderately to Severely Active Ulcerative Colitis."

The study was conducted in 51 study sites in 16 countries, most o which were European countries, but also in Canada, the US, and Korea.

The first subject was enrolled on 25th January 2016, and the last subject completed the trial on 1st November 2018. The data of the report is 30th July 2019 (with an amendment as of 9th July 2020)

The study was primarily designed as a safety study in order to evaluate the long-term safety and tolerability of etrasimod. Efficacy was considered a secondary objective with documenting of achieving and maintaining clinical response and/or remission.

To be eligible for this study, subjects must have completed the 12-week induction study APD334-003 and met the eligibility criteria for the APD334-005 extension study at the time of entry.

All subjects included received 2 mg etrasimod orally once daily for 34 weeks according to the initial study plan, but subjects who were enrolled under Protocol Amendment 2 (28 September 2015) received placebo or 2 mg etrasimod tablets once daily for 40 weeks.

Evaluation was mainly based on the Mayo Score evaluations, using the MMS and other partial Mayo Score evaluations, the biomarker CRP, and the IBDQ. The main endpoints were clinical response (end of treatment and both at the end of the precursor study and EoT), endoscopic improvement, endoscopic remission, RB and SF (and their combination), reduction of oral corticosteroid use, and changes from baseline in CRP, PGA, and other partial Mayo Score evaluations. Descriptive statistics were applied.

Subject disposition is shown in the following table:

Table 49: Subject disposition(all enrolled subjects) – Study APD334-005

	Previously Treated in APD334-003 (APD334-005 Treatment: 2 mg Etrasimod)			APD334-005 Treatment	
	Placebo (N=42) n (%)	1 mg Etrasimod (N=38) n (%)	2 mg Etrasimod (N=32) n (%)	2 mg Etrasimod (N=112) n (%)	Placebo (N=6) n (%)
Total number of subjects					
Enrolled	42 (100)	38 (100)	32 (100)	112 (100)	6 (100)
Completed study treatment	33 (78.6)	35 (92.1)	24 (75.0)	92 (82.1)	5 (83.3)
Discontinued study treatment	9 (21.4)	3 (7.9)	8 (25.0)	20 (17.9)	1 (16.7)
Adverse event	4 (9.5)	2 (5.3)	4 (12.5)	10 (8.9)	1 (16.7)
Lost to follow-up	0	0	0	0	0
Consent withdrawn	1 (2.4)	1 (2.6)	2 (6.3)	4 (3.6)	0
Investigator decision	0	0	0	0	0
Death	0	0	0	0	0
Sponsor decision	0	0	1 (3.1)	1 (0.9)	0
Other	4 (9.5)	0	1 (3.1)	5 (4.5)	0
Completed study	33 (78.6)	35 (92.1)	24 (75.0)	92 (82.1)	5 (83.3)
Discontinued study	9 (21.4)	3 (7.9)	8 (25.0)	20 (17.9)	1 (16.7)
Adverse event	2 (4.8)	1 (2.6)	2 (6.3)	5 (4.5)	0
Lost to follow-up	0	0	0	0	0
Consent withdrawn	1 (2.4)	1 (2.6)	2 (6.3)	4 (3.6)	1 (16.7)
Investigator decision	6 (14.3)	1 (2.6)	3 (9.4)	10 (8.9)	0
Death	0	0	0	0	0
Sponsor decision	0	0	1 (3.1)	1 (0.9)	0
Other	0	0	0	0	0

Source: Table 14.1.1.1.

The datasets analyse are displayed in the following table:

Table 50: Analysis Populations study APD334-005

Population/Cohort	Previously Treated in APD334-003 and Received 2 mg Etrasimod in APD334-005[d]			APD334-005 Treatment	
	Placebo	1 mg Etrasimod	2 mg Etrasimod	2 mg Etrasimod[d]	Placebo
MITT Evaluable Cohort[a] Same treatment	39	35	31	105	6[e]
MITT Mixed treatment Cohort[b]	3	3	1	7	0
Safety[c] Demographics and Safety	42	38	32	112	6

MITT = Modified Intent-to-Treat
[a] Subjects who received same study drug during APD334-005 study.
[b] Subjects who received mixed study drugs during APD334-005 study for any reason.
[c] Subjects who received at least 1 dose of study drug during APD334-005 study.
[d] Received any dose of 2 mg etrasimod during APD334-005.
[e] None of these subjects received etrasimod in APD334-005. Previous treatment in APD334-003: placebo (2 subjects), 1 mg etrasimod (1 subject), 2 mg etrasimod (3 subjects).
Sources: APD334-005 SAP; profile.sas, Listing 16.2.5.5, ADaM ADSL; Table S03; Table S04.

There was no primary efficacy endpoint in this study. For most subjects, EOT occurred at 46 weeks. For the subset of subjects enrolled under Protocol Amendment 2, the EOT occurred at 52 weeks. To include all data, the endpoint results are presented using EOT instead of Week 46.

The main outcome for clinical response is given in the following table, showing the subgroups according to pre-treatment, and according to treatment in -005.

Table 51: Proportion of Subjects Who Achieved or Maintained Clinical Remission at End of Treatment (Completers Population Evaluable Cohort) – Study APD334-005

	Previously Treated in APD334-003 (APD334-005 Treatment: 2 mg Etrasimod)			APD334-005 Treatment	
	Placebo (N=31)	1 mg Etrasimod (N=31)	2 mg Etrasimod (N=22)	2 mg Etrasimod (N=84)	Placebo (N=4)[b]
Clinical Remission at Week 12[a]					
n (%)	3 (9.7)	3 (9.7)	12 (54.5)	18 (21.4)	0
90% exact CI	[2.7, 23.2]	[2.7, 23.2]	[35.3, 72.9]	[14.3, 30.1]	[0.0, 52.7]
Clinical Remission at End of Treatment					
n (%)	11 (35.5)	11 (35.5)	11 (50.0)	33 (39.3)	1 (25.0)
90% exact CI	[21.3, 51.8]	[21.3, 51.8]	[31.1, 68.9]	[30.3, 48.8]	[1.3, 75.1]
Clinical Remission at Week 12 and End of Treatment					
n (%)	2 (6.5)	1 (3.2)	9 (40.9)	12 (14.3)	0
90% exact CI	[1.2, 18.9]	[0.2, 14.4]	[23.3, 60.5]	[8.5, 22.1]	[0.0, 52.7]

CI, confidence interval
Note: Evaluable cohort included subjects who received the same study drug treatment during APD334-005 study. Weeks were defined from start of Study APD334-003.
Clinical remission was defined as individual subscores of the adapted 3-component MCS as follows: an endoscopy score (using flexible proctosigmoidoscopy) of 0 or 1 (excluding friability), a rectal bleeding score of 0 or 1, and a stool frequency score of 0 or 1 with a decrease of ≥ 1 point compared with baseline of Study APD334-003.
[a] Clinical remission at Week 12 was used as the baseline for Study APD334-005.
[b] None of these subjects received etrasimod in APD334-005.
Source: Table 14.2.2.2; Table S03.

Further exploratory endpoints were generally in support of the remission endpoint. There seems to be good maintenance of effects over time, and patients previously treated with placebo or the lower dose of etrasimod appear to benefit relevantly from the switch to active treatment. A relevant increase in efficacy over time however, cannot be detected. Nevertheless, the study can overall be taken as supportive for the conclusion on efficacy.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

In support of efficacy, the applicant has presented 3 clinical studies, one phase 2 (study 003) dose-finding study, and two pivotal phase 3 trials (studies 301 and 302) which had an identical design with regard to the short-term treatment phase, but one of which included also a long-term "treat through" treatment period (study 301).

The design of the trials was considered overall adequate, especially with regard to the "pivotal" trials 003 and 302, since a "standard" duration of the trials of 12 weeks for this indication was used, and patients were randomised into equally sized active treatment groups (in study 003 with two doses).

The design of the main trial 301, which was the only study addressing the requirement of long-term efficacy had been considered non-standard during EMA scientific advice. Contrary to the "usual" design of the documentation of long-term efficacy, this trial used a so-called "treat-through" design which does not randomise the responders to an initial treatment phase only but leaves patients for the whole duration of 52 weeks within the initial randomisation groups. The overall design of the trial can be regarded to be appropriate and was in accordance with the scientific advise given even though the

design is not completely following the recommendation of the UC CHMP guideline to include an active control for the long-term treatment phase. Still, the pitfalls of such a design have become obvious during the conduct of the trial (see below).

The applicant has included formally a "standard" population of patients with ulcerative colitis which were pre-treated with either conventional therapy, including mesalazine, corticosteroids and "conventional" immunosuppressants, or biologics and/or JAK inhibitors. The inclusion criteria with regard to treatment were considered adequate, even though the inclusion of patients pre-treated with mesalazine only was allowed. However, the percentage of patients in this category was relatively small (overall 17% of patients in long-term and 11% in short-term study) and does not per se question the indication claim of a second and/or third-line therapy. However, patients with severe disease should usually not be treated with mesalazine only, since it is only indicated for mild to moderate disease.

Patients with isolated proctitis were also allowed to enter the study which is a special feature of the trial since usually, patients with proctitis only are excluded from trials in UC. These patients were included based on the same inclusion criteria as the patients with more extensive disease and the protocol did not define a proctitis-specific pre-treatment. This is considered inadequate considering that the cornerstone of treatment is locally applied 5-ASA and/or corticosteroids in addition to the systemic treatments. Although it is agreed that this subpopulation of UC patients is underrepresented in pivotal trials, the applicant was advised to evaluate those patients outside the primary analysis, however this was finally not done. There was finally 6.5% of those patients in the long-term study and 7.6% in the short-term study.

The patients were to suffer from moderate to severe disease, which was initially proposed to deviate from the "usual" criteria of having a MMS score of 5-9 with allowing also patients into the trial with an MMS of 4, but imposing an endoscopic subscore of at least 2 (MES=2). This was also discussed in advance of the study conduct, and in principle, the CHMP advice did not have objections since disease severity classification is an issue under debate, and the reassurance of having endoscopically a "moderate to severe" disease state was considered adequate. However, the applicant has finally evaluated the subgroup of patients with MMS 5-9 as the primary analysis population, which is also considered acceptable.

In accordance with sought indication, inclusion criteria allowed patients from 16 years of age to be included, however only 3 patients were included – one in ELEVATE UC 52 study (received placebo) and 2 in ELEVATE UC 12 study (one received etrasimod). There are no data from pivotal studies on efficacy of etrasimod in patients from 16 to 18 years of age, and the applicant has provided supportive argumentation and PKPD modelling data in support intended indication. For additional comments on PKPD modelling in regard to pursued indication, please see Pharmacology section.

Overall, the in- and exclusion criteria are partly not fully reflective of intended indication. However, the additional analyses in order to gain more clear presentation of efficacy in targeted population and "second line" treatment setting have overall not shown relevant reasons for concern.

The applicant has designated as primary endpoint the evaluation of "clinical remission" rates after 12 weeks (for both pivotal studies) defined as a composite of SF subscore = 0 (or = 1 with a ≥ 1 point decrease from Baseline), RB subscore = 0, and ES ≤ 1. This endpoint, however, is reflecting the guidance as required by the FDA, rather than complying with the European UC guidance. The applicant has assigned a number of 3 "key secondary endpoints" which were: Endoscopic improvement defined as an ES of 1 or 0 (excluding friability), symptomatic remission defined as an SF of 0 or 1 (in case there is an at least 1-point improvement) and RB=0, mucosal healing defined as ES of ≤ 1 (excluding friability) with histologic remission measured by a Geboes Index score < 2.0. While the primary endpoint – as mentioned – does not reflect the requirements of the CHMP UC guideline, the key secondary endpoints do acceptably cover the UC guideline requirements. The endpoint defining mucosal healing allowing a MES of 1 could be questioned but, considering that it is defined as a

composite including the histological normalisation, it can finally be accepted. The further secondary endpoints evaluating different categorisations of response, as well as improvement, and scales for additional symptoms, parameters of Quality of Life, and biomarkers were also considered adequate.

The evaluation of endoscopy (and of histology) was done by central reading with "standard" algorithms for evaluation and is considered fully acceptable.

For the long-term evaluation of efficacy in study 301 the primary evaluation for week 52, as well as most of the "key secondary" endpoints for 52 were the same as for the 12 week time-points of both studies. However, in addition to the 3 key secondary endpoints, 2 further "key secondary" endpoints were added, namely the proportion of subjects, in clinical remission at Week 52 and who had not been receiving corticosteroids for ≥ 12 weeks and the proportion of subject being in "sustained clinical remission" with the requirement to have been in clinical remission both at week 12, and week 52. In consequence, while the addition of the two additional "key secondary" endpoints can be accepted, the proposed primary endpoint is again not compliant with the CHMP UC guideline. Moreover, in the case of the week 52 evaluations, usually the requirement for "corticosteroid-free" evaluation of both mucosal healing, as well as symptomatic remission would be required, which was restricted to an evaluation of "clinical remission" defined as a composite of all three MMS components. The applicant included the "corticosteroid-free endoscopic improvement" with acceptable criteria as "other secondary endpoint", but only evaluated the "corticosteroid-free symptomatic remission" as a post-hoc endpoint. While this remains a point of criticism, the overall results are considered suitable and sufficiently robust to dispel the concerns with this endpoint not having been pre-planned.

The applicant has determined a clear estimand strategy as requested by the ICH E9 addendum which was for the most part in line with the requirements of the CHMP UC guideline. Since treatment discontinuations were also analysed with a composite strategy this needed further evaluation the induction part. Treatment discontinuation should normally be incorporated with a treatment policy strategy instead of the composite strategy applied by the applicant. However, for the majority of patients discontinuing treatment efficacy data are not evaluable post discontinuation. Hence, a sensible approach for estimation of different estimands for the primary and secondary endpoints is therefore not available, which is regrettable, but has to be accepted based on the limited availability of efficacy evaluations in those with intercurrent events/dropouts.

The observed high rate of IEs also somewhat hampers the evaluation and time-course of response.

The statistical methods, including sample size calculation were considered mostly adequate. However, the applicant has somehow missed to take full account of the high discontinuation rates expected (see below).

The applicant has conducted the studies during the years 2019 to 2022 and the study conduct was therefore affected by the Covid-19 pandemic. Despite some drawbacks, and necessary changes in the study protocol, the recruitment and conduct of the trial was not greatly affected by this.

The protocol for study 301 was amended several times with four global important changes, and several regional specific changes, two of which potentially contribute to the uncertainties: The change for the criteria for discontinuation (for "disease worsening") and those for the evaluation of patients being corticosteroid free. The effects of both amendments have been additionally evaluated and are overall not considered to bias the results in any way.

Overall, the trial design and the overall programme is considered suitable for the indication claimed.

Efficacy data and additional analyses

The achieved effects after 12 weeks of treatment were considered to be in the same range as reported for other substances in the clinical setting investigated. The rate of clinical responders with the definitions as of the applicant was between 30%-35% for the active treatment groups in the two

pivotal studies, while placebo treated patients had responder rates of 14-19% only. While the two studies do somewhat differ in the magnitude of the effects, the pooled estimations show an at least doubling of the rate, which is considered satisfactory. Overall, almost 50% of the patient do achieve a symptomatic remission with vast normalisation of the symptoms, and mucosal healing – identified as a predictor of long-term prognosis – is achieved in almost 20% of the patients. Around 15-17% of patients treated with etrasimod achieved endoscopic normalisation (ES=0, which would be compliant with EU guideline definition of endoscopic remission) compared to 4-8% in placebo group. Around 10 % of patients treated with etrasimod achieved very stringent (ad hoc) endpoint of endoscopic normalisation with histologic remission. At week 12, all primary, as well as the key secondary, and the vast majority of the other endpoints show high statistical significance.

For the week 52, based on the one pivotal study 301, the results also demonstrate high clinical significance throughout the primary and key secondary evaluations, as well as most of the additional secondary endpoints. At week 52, still about 44% of the patients are in symptomatic remission, and more than 26% have achieved mucosal healing (and almost 37% achieve corticosteroid free endoscopic improvement and were thus able to abandon intake of corticosteroids and have a widely normal mucosa), 44% also achieved corticosteroid free symptomatic remission. All these results were achieved with relevantly lower percentage by the placebo treated patients. The results included in these evaluations are therefore considered to be of high clinical relevance.

The original protocol defined being corticosteroid-free as" have not received corticosteroids for ≥ 12 weeks in the 40-Week Treatment Period". This was inadequate, so the applicant changed definition to "have not received corticosteroids for ≥ 12 weeks prior to Week 52" in the last protocol amendment, which is acceptable. Questions with regard to implementation of this change have been adequately addressed. The evaluations additionally conducted for the "corticosteroid-free" endpoints have overall shown robustness of the results.

The main drawback of the long-term study 301 and thus for the overall documentation of long-term efficacy is the fact that only about 32% of the patients completed the full study duration in the placebo group, whereas the rate of completers was 56% in the active treatment group. This is not per se a concern, also because it can be made clear that the rates of discontinuation obviously clearly reflect the loss of efficacy/response during the course of the study being clearly more pronounced in the placebo group. Furthermore, re-analysis using a more appropriate missing data handling approach (placebo based multiple imputation), support results of the original analysis. However, the evaluation of overall time-course of response is somewhat hampered by the high rates of IE leading to discontinuation and makes the conclusions on the long-term benefits somewhat difficult.

Despite these drawbacks, it is considered that the evaluations based on responder rates (with the composite estimand, and patients declared as non-responders when data were missing, irrespective of the reason) are considered an acceptable evaluation allowing a conclusion on efficacy. In addition, the reported reasons for discontinuation also speak in favour of the active treatment.

The results of sensitivity and supplementary analyses supported the primary results, both for the primary as well as for the "key secondary" endpoints, including a significantly greater proportion of subjects in the FAS (subjects with Baseline MMS 4 to 9) who achieved clinical remission at Week 12 and Week 52 with etrasimod compared with placebo.

While there is overall a convincing statistically significant superiority of the active treatment over placebo, it is also obvious that the number of patients going into remission early and remaining in remission until the end of the study period is under 20%, which means that for the vast majority of patients an only incomplete response, to treatment can be achieved. Also, over the 52 week treatment period, only about 25% achieve mucosal healing, which is thought to have an overall good prognosis for the long-term outcome. However, almost half of the patient population have a valuable clinical benefit on the main symptoms of UC.

While the overall results indicate efficacy for the overall study population, there were some uncertainties with regard to certain subgroups identified in the initial evaluation. However, the comprehensive evaluation of all clinically relevant subgroups provided at request has resolved these concerns to a wide extent including those patients having been "heavily pre-treated" (with more than one biologic/JAK inhibitor).

The presented additional analyses for excluding patients having received 5-ASA compounds only or suffering from proctitis only preserved high statistical significance for study 301. However, in study 302, statistically significant superiority of etrasimod over placebo was not demonstrated for endoscopic improvement or mucosal healing at week 12. The high placebo response in conjunction with baseline features of the patient population was identified as a reason for this phenomenon.

While the applicant claims the treatment of adolescents, and the two pivotal studies have been trying to recruit patients from the age of 16 and above, the number of patients aged below 18 at the time of inclusion was extremely low, with a total of 3 patients (of which 1 was in the etrasimod, and 2 in the placebo groups). Therefore, granting the indication in adolescents from 16 years of age is based on extrapolation from adult patients.

Although differences in disease severity between children and adults exist, the pathogenesis of UC and disease course can be considered sufficiently similar, and is more similar the older the children are, in order to allow extrapolation of efficacy from adults to older adolescents based on similar exposure of etrasimod.

According to the Pop PK analysis, no significant differences in etrasimod exposure are expected between older adolescents and adults with UC. Limited additional paediatric data (n=2) from the ongoing PIP study showed etrasimod steady-state exposure within the adult range.

Due to limited data in patients 16 to <18 years, the applicant provided additional analyses of efficacy, safety, PKPD and exposure-response, comparing young adults (≤25 years, n=101) to older adults (>25 years, n=642). Overall, responder rates at Week 12 appear generally similar between young adults and older adults, except for the endoscopic improvement that was less in the younger adults group. 52 week data come only from study APD334-301 with a high discontinuation rate of young adults (only 17 subjects ≤25 years completed the study). Thus, it is difficult to make an efficacy comparison at Week 52. Safety profile in general appears similar between the two groups. PK/PD modelling and exposure-response analyses did not suggest any clinically meaningful difference between younger and older adults. Thus, it can be agreed to include patients age 16 years or older in the indication. Due to the safety profile of the compound, patients with underlying infectious diseases, and with cardiovascular diseases have been excluded from the study programme. While this is a similar problem for all substances acting with any kind of immunosuppressive/-modulating effects, the exclusion of patients with CV disease (especially those with SA- and AV-block and being treated with antiarrhythmic medication, or in any kind influencing heart rhythm) is a special feature of SP1 modulators. The findings of the trials are therefore not generalizable to a population with co-existing heart disease and makes a restriction of the target population necessary. Adequate contraindications have been implemented in the SmPC on patients with co-existing heart disease and a warning is given that prior to treatment initiation with etrasimod, an electrocardiogram (ECG) should be obtained in all patients to assess for pre-existing cardiac abnormalities.

The applicant has evaluated the dose- and exposure response relation with a PK-PD modelling exercise. The available clinical data – especially all investigations with regard to the influence on the heart rate and the phase 2 study – support the applicant's choice of the 2 mg as the target dose. However, since response indicated a dependency on PK and this itself appeared to be dependent on body weight, a body weight-based strategy could have been possible, which was, however, not implemented for the sake of more convenient dosing. This is acceptable.

The applicant has included contraindications and warning statements into the chapters 4.3-4.5 of the SmPC in order to address class effects of the SP1 modulators and has partly included these statements in analogy to other compounds that have previously been licensed in this drug class (e.g. heart rate effects, effects on leukocyte/lymphocyte counts and their potential consequences). The substance is proposed to be used with full dose from the first day of treatment (with adequate precautions for surveillance of heart-rate related effects) which is based on the fact that several titration regimens tested did not overall reduce these effects.

There are currently a couple of clinical studies ongoing, especially for the Asian populations in Japan and China (these patient groups were somewhat underrepresented in the programme), but also open-label extension studies for which only part of the results could be presented at this stage of evaluation. At request, the applicant has presented the results of a study that has been completed during the assessment period. This study, is in principle a long-term study similar to study 301, included the Japanese patients from study 302 only. The patients were treated for 40 additional weeks with their original treatment assignment. In study 302, 48 Japanese patients were randomised, and of these 42 completed week 12. Completion of study was achieved with 4 (28.6%) in the placebo, and 18 (64.3%) patients in the active treatment group.

The results of the long-term extension for the Japanese patients were largely in accordance with the results of study 301 with effect sizes being partly greater than observed in study 301 even though overall statistical significance was not achieved.

2.6.7. Conclusions on the clinical efficacy

The applicant has presented an overall acceptable programme for the documentation of efficacy, and both of the trials presented for pivotal evidence have shown statistically significant and clinically relevant superiority of the treatment over placebo, with highly consistent results across the studies, different endpoints, and relevant subgroups. It is concluded that efficacy has been adequately substantiated. The applicant also demonstrated a corticosteroid sparing effect in study 301, which showed that both the duration and doses administered could be reduced on active treatment as compared to placebo supporting the results of the "corticosteroid-free" endpoints.

2.6.8. Clinical safety

The safety data package includes 20 completed (15 completed Phase 1, 3 completed Phase 2 (UC and atopic dermatitis [AD]), 2 completed pivotal Phase 3 (UC; Studies APD334 301 and APD334 302) and 3 ongoing Phase 2 or Phase 3 studies (UC and alopecia areata [AA]).

In total, safety database includes data from 1107 patients with UC, AD, or AA and 449 subjects from clinical pharmacology studies exposed to any dose of etrasimod.

The applicant has provided an integrated safety summary (ISS) that includes 6 different pools, 5 containing phase 2 and 3 studies and one Phase 1 studies. Data cut-off point is 31 January 2022. Ongoing blinded studies and blinded study periods were not included as the treatment assignment is unknown.

Safety in ISS is primarily based on 3 pools in subjects with UC (target population; phase 2 and 3 data): the Pivotal UC Pool, Placebo Controlled UC Pool (largest pool containing placebo-controlled UC data), and All UC Pool (includes largest portion of long-term treatment data).

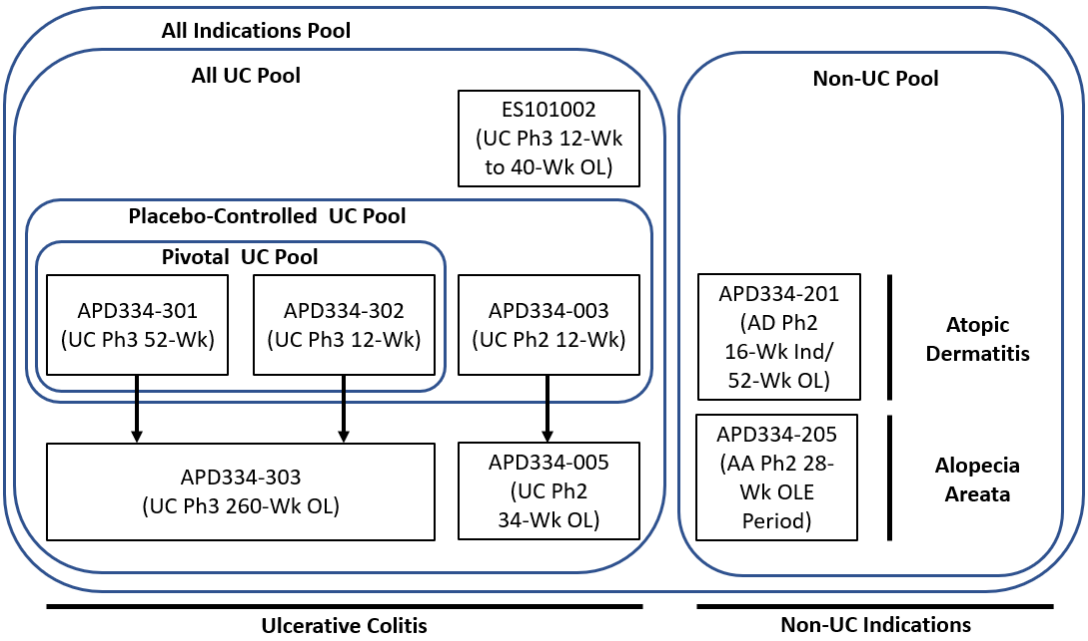


Figure 25: Pooling Strategy (phase 2 and 3 studies) for Integrated Analyses of Safety in the Etrasimod UC Submission

Note: Subjects in Study APD334-303 may enrol from parent studies not represented in this figure.

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

Safety was assessed by means of recording treatment emergent adverse events (TEAEs), vital signs, ECG/Holter monitoring, laboratory analyses, Optical Coherence Tomography (OCT) and pulmonary function tests (PFT).

TEAEs were presented by incidence rates and exposure-adjusted incidence rates (EAIR) by treatment. The latter defined as the number of subjects with AE divided by the total subject-years at risk for the AE (i.e., sum of individual time to first episode of AE onset, or time in the study if the subject was event-free). Severity, causal relationship, time-to-onset, duration, etc., have been analysed as per standard. Interpretation of EAIRs depends on the constant rate assumption (Scosyrev and Pethe, 2021) and since, this is not the case with etrasimod, EAIR data are not considered in the assessment.

Sponsor-designated Events of Interest (SDEIs) were additionally defined by the applicant using very narrow criteria. These are practically a sub-set of TEAEs, that, through selection, may disregard potentially relevant safety information. Therefore, this analysis is practically not presented in the assessment.

With the responses to the Day 120 LoQ the applicant submitted an updated All UC Pool and All Indications Pools (data cutoff of 30 August 2022), which included additional data from ongoing Studies APD334-303 and ES101002 (updated All UC Pool) and data from Studies APD334-303, ES101002, and APD334-205 open-label period (updated All Indications Pool), 1 new study and study population (Study APD334-202 in subjects with CD) not included in the initial ISS was also included in the updated All Indications Pool. Focus on this update is put on the All UC pool only as more relevant.

Throughout the safety part of this document "etrasimod" or "etrasimod 2 mg" is used interchangeable when referring to the treatment arm of 2 mg dose.

2.6.8.1. Patient exposure

As of the data cutoff for this application, 31 January 2022, etrasimod has been orally administered to 1556 subjects, including 1107 subjects with UC, AD or AA with 879.1 total subject-years of exposure to any dose of etrasimod.

Table 52: Summary of the safety data pools

	Etrasimod 2 mg/day	Etrasimod < 2 mg/day	Etrasimod > 2 mg/day	Etrasimod Any Dose	Placebo
Pools	(N=1378) n (%)	(N=256) n (%)	(N=78) n (%)	(N=1556) n (%)	(N=560) n (%)
Pivotal UC Pool	527 (38.2)	0	0	527 (33.9)	260 (46.4)
Placebo-Controlled UC Pool	577 (41.9)	52 (20.3)	0	629 (40.4)	314 (56.1)
All UC Pool	942 (68.4)	52 (20.3)	0	956 (61.4)	322 (57.5)
Non-UC Pool	135 (9.8)	47 (18.4)	18 (23.1)	151 (9.7)	46 (8.2)
All Indications Pool	1077 (78.2)	99 (38.7)	18 (23.1)	1107 (71.1)	368 (65.7)
Clinical Pharmacology Pool	301 (21.8)	157 (61.3)	60 (76.9)	449 (28.9)	192 (34.3)

Notes: Percentages are based on the number of subjects in the All Exposed Safety Analysis Set.
Subjects who received more than one study treatment or etrasimod dose level are summarised in all applicable treatment groups.
Source Data: Listing 16.1.1

In UC subgroup, 942 subjects contribute 757.9 total subject years of exposure to etrasimod 2 mg, with 666, 281, and 27 subjects exposed to etrasimod 2 mg for ≥ 26, ≥ 52, and ≥ 104 weeks, respectively. Placebo-controlled data on 2 mg etrasimod over at least 26 and 52 weeks treatment are available for 185 and 132 patients with UC, respectively (n = 56 and 40 patients on placebo).

Mean treatment durations with etrasimod in the pivotal and placebo-controlled pools were around 25 weeks vs. 19 weeks on placebo.

Mean exposures to etrasimod 2 mg in all UC and all indication pools were roughly about 42 weeks reflecting larger portion of non-controlled long-term data in these pools.

In the All UC Pool 666 subjects were exposed to etrasimod 2 mg for ≥ 26 weeks and 281 subjects for ≥ 52 weeks. The All UC Pool is the only pool with subjects exposed to etrasimod 2 mg for ≥ 104 weeks (27 subjects).

Exposure to etrasimod 2 mg in the All Indications Pool for ≥ 12 weeks, ≥ 26 weeks, ≥ 52, and ≥ 104 weeks was reported in 928, 743, 335, and 27 subjects, respectively.

In all pools (apart from the non-UC pool), exposure to etrasimod 2 mg was fairly well balanced in various subgroups (by gender, race, ethnicity and age), when duration of treatment was considered. Subgroup of elderly patients ≥65 years had much lower exposure when patient-years are regarded, consistent with the fact, that only limited number of elderly patients were included in the studies.

The majority of the population with UC included in the safety database was white, male, middle aged and Caucasian from Eastern Europe.

Only 3 adolescent patients (from 16 to <18 years) in total were tested, from these only 1 patient on etrasimod 2 mg and, as mentioned, the age group of ≥65 and ≥75 years olds is also underrepresented.

Reported baseline parameters for activity of the disease reflected the presence of UC of moderate to severe intensity. Population in different pools was well balanced as per baseline characteristics.

With the submitted update a total of 1051 subjects in the updated All UC Pool received any dose of etrasimod and had a combined 1106 total subject-years of exposure, an increase of 95 subjects and 336.7 subject-years over the initial All UC Pool exposure. Of these, 1037 subjects were exposed to the etrasimod 2 mg dose, which totals 1094.6 subject-years of exposure and is an increase of 95 subjects and 336.7 subject-years of exposure compared to the initial All UC Pool. 502 subjects had ≥ 52 weeks of exposure to the etrasimod 2 mg dose in the updated All UC Pool, and 117 subjects had ≥104 weeks of exposure, an increase of 221 subjects and 90 subjects over the initial All UC Pool, respectively.

A total of 1301 subjects in the updated All Indications Pool received any dose of etrasimod and had a combined 1243.2 total subject-years of exposure, an increase of 194 subjects and 364.1 subject-years over the initial All Indications Pool exposure, with 556 subjects having ≥ 52 weeks of exposure, and 117 subjects treated ≥104 weeks.

Demographic characteristics were similar between the initial and updated All UC and All Indication Pools.

2.6.8.1. Adverse events

Placebo-Controlled UC Pool Summary

The proportion of subjects with at least 1 TEAE was similar in both etrasimod groups (etrasimod 2 mg: 346 subjects, 60.0%, EAIR 2.34; etrasimod < 2 mg: 31 subjects 59.6%, EAIR 4.06) and greater compared to placebo (162 subjects, 51.6%, EAIR 2.24) (Table 53)

Table 53: Overall Summary of Treatment-Emergent Adverse Events (Placebo-Controlled UC Pool)

Subjects With at Least 1	**Etrasimod 2 mg/day (N=577) n (%) [EAIR]**	**Etrasimod < 2 mg/day (N=52) n (%) [EAIR]**	**Etrasimod Any Dose (N=629) n (%) [EAIR]**	**Placebo (N=314) n (%) [EAIR]**
TEAE	346 (60.0) [2.34]	31 (59.6) [4.06]	377 (59.9) [2.43]	162 (51.6) [2.24]
Related TEAE	81 (14.0) [0.32]	4 (7.7) [0.35]	85 (13.5) [0.32]	24 (7.6) [0.22]
Any Grade 3 or Higher TEAE	31 (5.4) [0.11]	2 (3.8) [0.17]	33 (5.2) [0.11]	19 (6.1) [0.17]
Any Grade 3 or Higher Related TEAE	1 (0.2) [<0.01]	0	1 (0.2) [<0.01]	2 (0.6) [0.02]
SAE	26 (4.5) [0.09]	3 (5.8) [0.25]	29 (4.6) [0.10]	17 (5.4) [0.15]
Related SAE	1 (0.2) [<0.01]	1 (1.9) [0.08]	2 (0.3) [<0.01]	1 (0.3) [<0.01]
TEAE Leading to Treatment Discontinuation	29 (5.0) [0.10]	3 (5.8) [0.25]	32 (5.1) [0.11]	8 (2.5) [0.07]
Related TEAE Leading to Treatment Discontinuation	16 (2.8) [0.06]	1 (1.9) [0.08]	17 (2.7) [0.06]	2 (0.6) [0.02]

Subjects With at Least 1	Etrasimod 2 mg/day (N=577) n (%) [EAIR]	Etrasimod < 2 mg/day (N=52) n (%) [EAIR]	Etrasimod Any Dose (N=629) n (%) [EAIR]	Placebo (N=314) n (%) [EAIR]
Cardiac TEAE Leading to Treatment discontinuation	6 (1.0) [0.02]	0	6 (1.0) [0.02]	0
Liver-related TEAE Leading to Study Treatment Discontinuation	2 (0.3) [<0.01]	2	2 (0.3) [<0.01]	1 (0.3) [<0.01]
TEAE Leading to Study Treatment Interruption	25 (4.3) [0.09]	0	25 (4.0) [0.09]	8 (2.5) [0.07]
TEAE Leading to Death	0	0	0	0
SDEI	41 (7.1) [0.15]	1 (1.9) [0.08]	42 (6.7) [0.15]	15 (4.8) [0.13]

Percentages are based on the number of subjects in the pool.

Subjects are counted only once per summarisation level per treatment group.

Source: ISS Table 14.3.1.1.2

SOCs with higher incidence rates on etrasimod 2 mg by >1% compared to placebo were the following: Infections and infestations (19.1% vs. 16.6%), Investigations (12.8% vs. 8.9%), Nervous system disorders (12.1% vs. 6.7%), Musculoskeletal and connective tissue disorders (9.7% vs. 6.4%), Metabolism and nutrition disorders (6.6% vs. 2.9%), Eye disorders (5.0% vs. 3.2%), Cardiac disorders (4.2% vs. 1.3%), Vascular disorders (3.3% vs. 2.2%), Injury, poisoning and procedural complications (2.8% vs. 1.6%), Psychiatric disorders (2.3% vs. 1.3%), Hepatobiliary disorders (1.9% vs. 0.6%), and Reproductive system and breast disorders (1.0% vs. 0%).

The TEAEs (by PT) occurring in ≥ 1% of subjects in the etrasimod 2 mg group and that were more frequent (by ≥ 1% point) in the etrasimod 2 mg group compared to placebo were Headache, Pyrexia, Nausea, Dizziness, Gamma-glutamyltransferase increased, Hypertension, Urinary tract infection, Alanine aminotransferase increased, Vomiting, Blood creatine phosphokinase increased, Diarrhoea, Hypercholesterolaemia, and Bradycardia (Table 54). Additionally, a total of 7 participants (1.2%) out of 577 which can be grouped under the term "lower respiratory tract infections" were identified during the review (4 with Bronchitis, and 3 with PTs Pneumonia, Pneumonia viral, or Pneumonia bacterial, 1 event each) in the etrasimod 2 mg group. No such events were reported on placebo.

No pattern of dose dependence in the most frequently reported TEAEs (by PT) was identified; a limitation of this evaluation is the sample size and exposure duration (ie, 12-weeks versus 52-weeks based on study design) of the etrasimod < 2 mg group (Table 54)

Table 54: Treatment-Emergent Adverse Events Occurring in ≥ 1% of Etrasimod 2 mg Group Subjects by Preferred Term (Placebo-Controlled UC Pool; TEAEs with ≥ 1% higher incidence on etrasimod 2 mg than on placebo are highlighted in grey)

Preferred Term	**Etrasimod 2 mg/day (N=577) n (%) [EAIR]**	**Etrasimod < 2 mg/day (N=52) n (%) [EAIR]**	**Etrasimod Any Dose (N=629) n (%) [EAIR]**	**Placebo (N=314) n (%) [EAIR]**
Subject with at Least 1 TEAE	346 (60.0) [2.34]	31 (59.6) [4.06]	377 (59.9) [2.43]	162 (51.6) [2.24]
Anaemia	41 (7.1) [0.15]	2 (3.8) [0.17]	43 (6.8) [0.15]	24 (7.6) [0.21]
Headache	38 (6.6) [0.14]	0	38 (6.0) [0.13]	10 (3.2) [0.09]
Colitis ulcerative	33 (5.7) [0.12]	5 (9.6) [0.43]	38 (6.0) [0.13]	18 (5.7) [0.16]
Pyrexia	24 (4.2) [0.09]	0	24 (3.8) [0.08]	10 (3.2) [0.09]
COVID-19[a]	23 (4.0) [0.08]	0	23 (3.7) [0.08]	12 (3.8) [0.11]
Nausea	20 (3.5) [0.07]	1 (1.9) [0.08]	21 (3.3) [0.07]	6 (1.9) [0.05]
Arthralgia	19 (3.3) [0.07]	1 (1.9) [0.08]	20 (3.2) [0.07]	8 (2.5) [0.07]
Dizziness	18 (3.1) [0.06]	1 (1.9) [0.08]	19 (3.0) [0.07]	2 (0.6) [0.02]
Abdominal pain	14 (2.4) [0.05]	2 (3.8) [0.17]	16 (2.5) [0.05]	10 (3.2) [0.09]
Gamma-glutamyltransferase increased	12 (2.1) [0.04]	1 (1.9) [0.08]	13 (2.1) [0.04]	2 (0.6) [0.02]
Hypertension	12 (2.1) [0.04]	1 (1.9) [0.08]	13 (2.1) [0.04]	3 (1.0) [0.03]
Urinary tract infection	12 (2.1) [0.04]	2 (3.8) [0.17]	14 (2.2) [0.05]	3 (1.0) [0.03]
Alanine aminotransferase increased	11 (1.9) [0.04]	0	11 (1.7) [0.04]	2 (0.6) [0.02]
Back pain	11 (1.9) [0.04]	1 (1.9) [0.08]	12 (1.9) [0.04]	3 (1.0) [0.03]
Vomiting	11 (1.9) [0.04]	0	11 (1.7) [0.04]	2 (0.6) [0.02]
Blood creatine phosphokinase increased	10 (1.7) [0.04]	1 (1.9) [0.08]	11 (1.7) [0.04]	2 (0.6) [0.02]

Preferred Term	Etrasimod 2 mg/day (N=577) n (%) [EAIR]	Etrasimod < 2 mg/day (N=52) n (%) [EAIR]	Etrasimod Any Dose (N=629) n (%) [EAIR]	Placebo (N=314) n (%) [EAIR]
Abdominal distension	9 (1.6) [0.03]	0	9 (1.4) [0.03]	3 (1.0) [0.03]
Diarrhoea	9 (1.6) [0.03]	0	9 (1.4) [0.03]	1 (0.3) [< 0.01]
Fatigue	9 (1.6) [0.03]	1 (1.9) [0.08]	10 (1.6) [0.03]	3 (1.0) [0.03]
Flatulence	9 (1.6) [0.03]	0	9 (1.4) [0.03]	2 (0.6) [0.02]
Hypercholesterolaemia	8 (1.4) [0.03]	0	8 (1.3) [0.03]	0
Rash	8 (1.4) [0.03]	0	8 (1.3) [0.03]	4 (1.3) [0.03]
Asthenia	7 (1.2) [0.02]	0	7 (1.1) [0.02]	3 (1.0) [0.03]
Haemorrhoids	7 (1.2) [0.02]	0	7 (1.1) [0.02]	2 (0.6) [0.02]
Nasopharyngitis	7 (1.2) [0.02]	2 (3.8) [0.17]	9 (1.4) [0.03]	10 (3.2) [0.09]
Upper respiratory tract infection	7 (1.2) [0.02]	4 (7.7) [0.36]	11 (1.7) [0.04]	5 (1.6) [0.04]
Bradycardia	6 (1.0) [0.02]	0	6 (1.0) [0.02]	0
Respiratory tract infection viral	6 (1.0) [0.02]	0	6 (1.0) [0.02]	2 (0.6) [0.02]

[a] Study APD334-003, which is the only UC study that administered an etrasimod dose < 2 mg, was completed in 2018, prior to the start of the COVID-19 pandemic. No subjects at the etrasimod < 2 mg dose level are therefore expected to have experienced TEAEs of COVID-19.

TEAE is defined as AE that started after the first dose of study treatment. TEAE is associated with the treatment most recently received by the subject at the time of onset. Terms are coded using MedDRA v 24.1.

EAIR is defined as the number of subjects with AE divided by the total subject-years at risk for AE (sum of individual time to first episode of AE, or time in the study if subject was event-free). EAIR is presented per 1 subject-years

Adverse events are sorted by decreasing frequency of preferred term, in the etrasimod 2 mg/day treatment group.

Percentages are based on the number of subjects in the pool.

Subjects are counted only once per summarisation level per treatment group.

Source: ISS Table 14.3.1.12.2

- Severity of TEAEs

Most TEAEs were Grade 1 or 2 in severity in all treatment groups. The proportion of subjects with SAEs or any Grade 3 or higher TEAE, was generally similar across etrasimod 2 mg (4.5% and 5.4% of subjects, respectively), etrasimod <2 mg (5.8% and 3.8% of subjects, respectively), and placebo groups (5.4% and 6.1% of subjects, respectively) (Table 53)

The most frequent Grade 3 TEAEs by SOC (> 1% of subjects in any treatment group) with higher incidence rate on etrasimod 2 mg were Gastrointestinal disorders SOC (etrasimod 2 mg: 2.6% of subjects; etrasimod <2 mg: 3.8% of subjects; placebo: 1.9% of subjects) with PTs on etrasimod 2 mg: Colitis ulcerative, Nausea, Abdominal pain, Vomiting, Mucosal prolapse syndrome, and Proctitis; Blood and lymphatic system disorders SOC (etrasimod 2 mg: 0.9% of subjects; etrasimod <2 mg: no subjects; placebo: 1.3% of subjects) with PTs on etrasimod 2 mg of Anaemia, Iron deficiency anaemia, and Infections and infestations (etrasimod 2 mg: 0.5% of subjects; etrasimod < 2 mg: no subjects; placebo: 1.6% of subjects) with PTs in the etrasimod 2 mg group of COVID-19, COVID-19 pneumonia, and Pneumonia bacterial.

Two subjects each in the etrasimod 2 mg and placebo groups had a Grade 4 TEAE: Etrasimod 2 mg: Lymphopenia, Coronary artery disease; Placebo: Alanine aminotransferase increased, Duodenal ulcer perforation.

No subjects experienced Grade 5 TEAEs in this pool.

- Causal relationship

Related TEAEs were more frequent in the etrasimod 2 mg group (etrasimod 2 mg: 81 subjects, 14%, EAIR 0.32; etrasimod <2 mg: 7 subjects, 7.7%, EAIR 0.35; placebo: 24 subjects, 7.6%, 0.22).

The most frequently reported related TEAEs by SOC (≥2% of subjects in any treatment group) were Nervous system disorders, Investigations, and Gastrointestinal disorders, and by PT (≥ 1% of subjects in any treatment group) - Dizziness (etrasimod 2 mg: 1.7%, etrasimod < 2 mg: 0, placebo: 0.3%), Headache (etrasimod 2 mg: 1.0%, etrasimod < 2 mg: 0, placebo: 0.3%), and Nausea (etrasimod 2 mg: 1.0%, etrasimod < 2 mg: 0, placebo: 0.3%).

- Time-to-onset

Time-to-onset was calculated only for common TEAEs as defined in the SAP, i.e. TEAE with incidence rate of at least 1% and with higher frequency on etrasimod (any dose) than on placebo.

Median time to first onset was between 14 to 56 days (ie, 2-8 weeks) for approximately half of the SAP-defined common TEAE PTs.

Median time to first onset ≤28 days in the etrasimod 2 mg was reported for Dizziness (5 days vs 77 days on placebo), Asthenia (9 days vs. 65 days on placebo), Headache (14 days vs. 20.5 days on placebo), Abdominal distension (16 days vs. 29 day on placebo), and Upper respiratory tract infection (23 days vs 53 days on placebo).

Pivotal UC Pool Summary

This is a sub-set of the placebo-controlled pool. A similar profile of TEAEs was observed as for the Placebo-Controlled UC Pool.

All UC Pool Summary

The proportion of subjects with TEAEs (67.4% vs. 60%), with related TEAEs (25.3% vs. 14%), TEAEs of Grade 3 or higher (9.6% vs. 5.4%), SAEs (7.1% vs. 4.5%), TEAEs leading to treatment

discontinuation (6.6% vs. 5%) was greater in this pool compared to placebo-controlled pool and on etrasimod 2 mg.

TEAEs of Lymphopenia, Lymphocyte count decreased, Leukopenia, T-lymphocyte count decreased, Neutropenia, and White Blood cell count decreased were more frequently reported in the All UC Pool relative to the Placebo-Controlled and Pivotal UC Pools, which only included placebo-controlled studies.

Table 55: Treatment-Emergent Adverse Events Occurring in ≥ 1% of Etrasimod 2 mg Group Subjects by Preferred Term (All UC Pool; Cases with TEAEs reported first time on etrasimod 2 mg, or reported with higher incidence rate by≥ 1% compared to Etrasimod 2 mg in Placebo-controlled pool are highlighted in grey)

Preferred Term	**Etrasimod 2 mg/day (N=942) % (EAIR)**	**Etrasimod < 2 mg/day (N=52) % (EAIR)**	**Placebo (N=322) % (EAIR)**
Subject with at Least 1 TEAE	635 (1.82)	31 (4.09)	170 (2.26)
Colitis ulcerative	9.8 (0.12)	9.6 (0.43)	6.8 (0.18)
COVID-19	7.7 (0.10)	0 (0)	3.7 (0.10)
Lymphopenia	7.1 (0.09)	0 (0)	7.0 (0.09)
Lymphocyte count decreased	3.9 (0.05)	0 (0)	0 (0)
Upper respiratory tract infection	3.5 (0.04)	7.7 (0.36)	1.6 (0.04)
Leukopenia	1.7 (0.02)	0 (0)	0 (0)
T-lymphocyte count decreased	1.5 (0.02)	0 (0)	0 (0)
Neutropenia	1.2 (0.01)	0 (0)	0 (0)
Respiratory tract infection	1.1 (0.01)	0 (0)	0 (0)
White blood cell count decreased	1.1 (0.01)	0 (0)	0 (0)

Majority (90%) of TEAEs had severity level of 1 or 2. As in the Placebo Controlled UC Pool, the most frequent Grade 3 TEAEs by SOC were in the Gastrointestinal disorders SOC, Blood and lymphatic system disorders SOC, and Infections and infestations SOC. One Grade 5 (fatal) TEAE was reported for 1 subject in the etrasimod 2 mg group.

Drug-related TEAEs were not summarised for this pool, as the data include also unblinded information.

There was no clinically meaningful change in the EAIR or proportion of subjects who experienced TEAEs, TESAEs, or TEAEs leading to permanent or temporary discontinuation in the updated All UC pool compared with the initial pool.

Other Pools Summary

The TEAE profile for the All Indications Pool was generally similar to the 3 UC Pools as most subjects in the All Indications Pool also contribute to the All UC Pool. For the All Indications Pool in which etrasimod > 2 mg dose was administered only in non-UC studies, in the initial submission, 9 subjects (50%) experienced TEAEs compared with 47 subjects (63.5%) in the updated All Indications Pool.

Compared to the Placebo-Controlled UC Pool, the proportion of etrasimod-treated subjects with ≥1 Grade 3 or higher TEAE was greater in the Non-UC Pool.

TEAEs per organ system class or group of interest

Considering the mechanism of action of etrasimod and experience with other substances acting on S1P TEAEs reported in selected SOC have been presented and discussed separately in the pivotal UC pool (as the best pool with homogeneous phase 3 UC population) and all indications pool (as the largest pool). All indication pool is only mentioned if potentially relevant additional findings were reported. SDEI were summarised, but mostly represent a sub-set of TEAEs and are only briefly presented.

Cardiovascular disorders

Subjects with relevant cardiovascular pathologies were excluded from clinical studies. Those included were monitored in the clinic upon treatment initiation and for re initiation for at least 4 hours and up-to the second day of treatment depending on changes in vital signs/ECG parameters.

Pivotal UC pool: Cardiovascular TEAEs were reported more often on etrasimod 2 mg compared to placebo (38 subjects [7.2%] vs. 8 [3.1%]. The following events were reported in at least 2 patients (n (%) on etrasimod vs. placebo: Bradycardia 5 (0.9%) vs. 0, Sinus bradycardia 4 (0.8%) vs. 0, Atrioventricular block first degree 2 (0.4%) vs. 0, Hypertension 12 (2.3%; Note: includes "hypertensive crisis") vs. 3 (1.2%, Note: includes "essential hypertension"), Varicose vein 2 (0.4%) vs. 0. Additional TEAEs reported on etrasimod 2 mg in 1 subject each, but not on placebo (similar PTs are also considered, e.g. "venous thrombosis" and "deep vein thrombosis") were: atrial fibrillation, AV block second degree, cardiac failure chronic, coronary artery disease, sinus arrhythmia, sinus tachycardia, ventricular extrasystoles, flushing, hot flush.

Additional PTs reported for cardiovascular TEAEs in the all indications pool were: Myocardial ischaemia and supraventricular extrasystoles, Vascular events: Arteriosclerosis, Haematoma, Peripheral arterial occlusive disease, Peripheral coldness.

Proportion of most frequent cardiac and vascular TEAEs (e.g. bradycardia, sinus bradycardia, AV block first and second degree, hypertension, etc.) did not change in frequency on etrasimod 2 mg and in the all indications pool compared to the pivotal pool.

Cardiac TEAEs on Day 1 and Day 2-14:

In the pivotal UC pool half of the patients with cardiac events (n=11; 2.1%) had their first cardiac TEAE reported on the first day of treatment with etrasimod 2 mg: bradycardia (4 subjects), sinus bradycardia (4 subject), AV block first degree (2 subject), AV block second degree (1 subject) and sinus arrhythmia (1 subject). None such events were reported on placebo.

On Days 2-14: bradycardia (2 subjects) and palpitations (2 subjects; reported also on placebo) were observed.

In All indications pool similar proportion (2.2%) of patients on etrasimod had the same events reported on day 1 of the treatment with additional TEAE of ventricular extrasystoles (2 subjects). None of these events occurred on placebo.

On Days 2-14: One case of additional TEAE (compared to the pivotal pool – etrasimod 2 mg group) of atrial fibrillation occurred on day 2 of etrasimod treatment in the all indications pool.

Eye disorders

Subjects with a history of macular oedema or retinopathy were excluded from studies.

Macular oedema SDEI was monitored by an increase in central foveal thickness (CFT) > 40µm or by associated symptoms or clinically significant abnormal objective findings.

The proportion of subjects with TEAEs in the Eye disorders SOC was higher on etrasimod 2 mg compared to placebo in the pivotal pool (26 subjects, 4.9% vs. 9 subjects, 3.5%).

The proportion of subjects with event Macular oedema in the Pivotal UC Pool was the same (0.4% of subjects) in both etrasimod 2 mg and placebo groups, but 2 subjects had TEAE PTs of Cystoid macular oedema additionally, one in the updated All UC Pool and one in the all Indications Pool.

The most frequently reported (at least 2 patients on etrasimod 2 mg and not reported on placebo) TEAE PTs in the Pivotal UC Pool were Vision blurred, Blepharitis, Myopia, Papilloedema, Uveitis, and Visual Impairment. PC UC Pool: 5 participants (0.9%, EAIR 0.02) who received etrasimod 2 mg experienced 6 TEAEs of Vision blurred (none in placebo). Review of the events related to impaired vision in the PC UC Pool revealed that 9 cases of various events including 5 cases of "Vision blurred", 2 – "Visual impairment", 1 – "Visual snow" and 1 – Diplopia were reported on etrasimod (1.6%, assuming that each event was reported in different patient) and only one event of "Visual acuity reduced" was reported on placebo (0.3%).

The most frequently reported TEAE PTs (2 or more patients) on etrasimod 2 mg in the All Indications included TEAE PTs of Cataract, Vision blurred, Blepharitis, Dry eye, Glaucoma, Myopia, Papilloedema, Uveitis, Visual impairment, Astigmatism, Conjunctival haemorrhage, Conjunctivitis allergic, Eye pain, Keratitis, and Pigment dispersion syndrome.

Papilloedema

A 20- to 30-year-old male participant experienced a TEAE (mild, Grade 1) of Papilloedema (verbatim: swollen optic disc) on Study Day 83. At Screening, ophthalmology exams showed the participant had normal CFT results for both eyes. On Study Day 83, CFT results were and corrected visual acuity were normal. IOP was not performed. A dilated fundus exam showed a swollen optic disc, abnormal, clinically significant. No abnormalities were detected in slit lamp exam, the cornea was normal, anterior chamber was also normal. Study treatment was not changed, and no treatment was given for the event which was not resolved. The investigator assessed the event as related to study treatment.

A 40- to 50-year-old male participant experienced a TEAE (moderate, Grade 2) of Papilloedema (verbatim: papilloedema of left eye) on Study Day 330 that led to interruption of study treatment and was assumed to be related to trauma The event of papilloedema resolved on Study Day 349; the participant resumed study treatment. The event was assessed as not related to study treatment by the investigator.

A 50- to 60-year-old male participant experienced a TEAE (mild, Grade 1) of Papilloedema on Study Day 66 in Study APD334-303 that led to study treatment interruption. Relevant concomitant medications included ongoing prednisone, paracetamol, and iron. On Day 90 in the APD334-301 study, the participant had abnormal clinically significant right eye optic nerve swelling that had progressed toward the macula. Corrected visual acuity (right/left/combined) was 20/20. Dilated fundus examination and retinal photographs showed clinically significant right eye nerve swelling. Eye pressure exams were normal. The participant experienced a concurrent TEAE of Anaemia (Study Days 56 to 168) and a TEAE of Cerebral small vessel ischaemic disease (Study Day 71 and ongoing). No treatment was given for the event which resolved on Study Day 126 and was assessed by the investigator as not related to study treatment. The retinal specialist considered the underlying aetiology of the event to be due to anaemia and the underlying disease.

Additionally, one case of optic disc volume increased was reported in association of the SAE of intracranial pressure increased (in a 60-to 69-year-old male participant /study days 90 – 243). The

event of high intracranial pressure was considered resolved with sequelae of ocular nerve atrophy and partial vision loss. The investigator assessed the event to be unlikely related to study treatment. The applicant agreed with the investigator's assessment of relationship to study treatment.

Glaucoma

Overall, four (0.4%) participants who received etrasimod 2 mg (one patient being in the PC UC Pool; 0.2%, EAIR < 0.01) and 1 (0.3%, EAIR < 0.01) participant in the placebo group experienced TEAEs of Glaucoma were reported in the updated All UC pool. All events started later on treatment (282 and longer on etrasimod) and all were considered not drug related.

Respiratory, Thoracic and Mediastinal Disorders

Subjects were excluded if they had FEV_1 or FVC < 70% of predicted values and FEV_1/FVC ratio < 0.70 at Screening.

In pivotal UC pool proportion of patients with at least one TEAE in this SOC was similar across etrasimod 2 mg and placebo (3.2% vs. 3.8% respectively). TEAE PTs reported by ≥ 2 subjects on etrasimod, but not reported on placebo included Dyspnoea, Rhinorrhoea, Dyspnoea exertional, Nasal congestion, Rhinitis allergic. No TEAEs of Dyspnoea or Dyspnoea exertional were associated with clinically relevant decreases in PFT results; all events were mild, and no interventional treatment was administered, excluding in 1 subject who also had a concurrent TEAE of COVID 19. One subject with a TEAE of Dyspnoea of moderate severity study APD334-302reported a TEAE of COVID 19 that started the same day, resolved after the dyspnoea; the subject received inhaled salbutamol.

In All Indications Pool percentage of subjects with at least one TEAE was similar on etrasimod 2 mg (4.0%). The most frequently reported PTs (ie, experienced by ≥ 2 subjects and not reported on placebo) additionally included Atelectasis.

One relevant event, as defined by the applicant (SDEI) occurred in one patient (Study APD334 301 Subject in his 20's), who developed a Grade 1 decrease in Forced expiratory volume. No action was taken with study treatment, and the subject had not recovered as of the last available report at the data cutoff date. The subject continued in OLE Study APD334 303.

Infections and infestations

For inclusion in the Pivotal UC studies subjects were required to have adequate haematological function defined by WBC count $\geq 3.5\times10^9$ cells/L with ANC $\geq 1.5\times10^9$ cells/L, ALC$\geq 0.8\times10^9$ cells/L, platelet count $\geq 100\times10^9$ cells/L, and haemoglobin ≥8g/dL. Subjects were also excluded if they had conditions associated with a higher risk of serious or opportunistic infection.

A combination of serial lab assessments, with specific clinical monitoring for infection, including progressive multifocal leukoencephalopathy (PML) were applied in the studies. A PML Case Evaluation Algorithm indicating the sequence of events and parties involved in the evaluation of potential cases of PML was applied, which includes an independent PML adjudication committee.

Proportion of patients with such events was similar between etrasimod and placebo and in pivotal UC and all indications pool. Pivotal UC Pool, etrasimod 2 mg group: 99 subjects, 18.8%, EAIR 0.41 compared to placebo: 46 subjects, 17.7 %, EAIR 0.52. All Indications Pool, etrasimod 2 mg: 267 subjects, 24.8%, EAIR 0.36; etrasimod < 2 mg: 18 subjects, 18.2%, EAIR 0.79; etrasimod > 2 mg: 3 subjects, 16.7%, EAIR 0.55; placebo: 62 subjects, 16.8%, EAIR 0.53.

Majority of the reported PTs was COVID-19 related PT across treatments and pools and majority of TEAEs were unique TEAEs in single patients.

In the pivotal UC pool, TEAE PTs reported by ≥ 2 subjects on etrasimod 2 mg and no/lower proportion of subjects on placebo were Cystitis, Anal abscess, Bronchitis, Hordeolum, Pharyngitis, Clostridium difficile infection, Pustule, Rhinitis.

Clostridium difficile infection, COVID-19, Herpes simplex meningitis and Latent tuberculosis led to study discontinuation on etrasimod 2 mg and in UC population.

SDEI: Generally, no relevant differences in the proportion of patients with the subcategories of Herpes simplex and herpes zoster, severe infections (Grade≥ Grade 3) and opportunistic infections were detected.

Relevant cases leading to study discontinuation

Study APD334-303 a Subject with UC in his 60's had an **SAE** Herpes simplex meningitis on Study Day 12 that led to **permanent study treatment discontinuation** and was considered an **SDEI**, etrasimod 2 mg group (Grade 1, not related, dose withdrawn, recovered/resolved)

Study APD334-301 a Subject with UC in his 30's has a **TEAE** of Clostridium difficile infection on Study Day 5 leading to **permanent study treatment discontinuation**, etrasimod 2 mg group (Grade 1, not related, dose withdrawn, resolved)

In the updated All Indications Pool, 7 additional subjects in the etrasimod 2 mg group and 1 additional subject in the > 2 mg group experienced SDEI in the Severe infections category. All unlikely/not related to etrasimod. In this pool 2 additional subjects in the etrasimod 2 mg group experienced SDEI in the Herpes simplex and herpes zoster category. Both considered probably related by the investigator.

Opportunistic infections

Herpes-related events

In the PC UC Pool, a total of 10 participants experienced herpes-related events (Herpes Zoster, Herpes Simplex, Post-herpetic neuralgia, oral herpes) in the PC UC Pool; 7 participants (1.2%) were in the etrasimod 2 mg group (none in the etrasimod <2 mg group) and 3 participants (1%) were in the placebo group.

In the updated All UC Pool (data cut-off 30 August 2022) a total of 19 participants experienced herpes events (15 participants in the etrasimod 2 mg group and 4 in the placebo group), including the SAE of Herpes Simplex meningitis. No relevant difference in the frequency of these events were noted.

Clostridium difficile infection

In the PC UC Pool three TEAEs of clostridium difficile infection and one of Clostridium difficile colitis were reported on etrasimod with zero event on placebo.

Cytomegalovirus infection

In the PC UC Pool two events of cytomegalovirus infection were reported on etrasimod with zero events on placebo.

One event of cytomegalovirus infection (Study APD334-302) developed on day 36 in the study after discontinuation of etrasimod on day 20 and another on day 265 (Study APD334-303) after the event of lymphopenia. The second event was considered drug related by the investigator and led to treatment discontinuation. Both events are considered not drug-related by the applicant due to the presence of multiple confounders, such as concomitant treatments impacting immune defence.

Tuberculosis infection

One event of tuberculosis was reported on placebo with no event on etrasimod in the PC UC pool.

However, two cases of tuberculosis were registered on etrasimod in the open-label studies not included in the PC UC pool.

One case of tuberculosis developed in a young patient (Study APD334-301) without relevant medical history or concomitant medications, who lived in the endemic location for tuberculosis, on day 40 of treatment with etrasimod. Interferon-gamma release assay was negative and chest x-ray was normal at screening. No contact with infected person was reported. Lymphocyte count at the visit closest to the event start (day 15) was normal. The patient started treatment and discontinued etrasimod.

The second events of latent tuberculosis (Study APD334-303) developed on Day 392 of etrasimod 2 mg treatment. Ongoing medical history included anaemia. Concomitant medications ongoing at the onset of the AE of latent tuberculosis was mesalazine and methylprednisolone was periodically used during the study, but it was not ongoing at the time of the event.

Both events of tuberculosis were considered as unlikely/not related by the applicant.

Candida infections

In the PC UC pool 2 cases of candida infection on etrasimod and 1 on placebo were observed.

Hepatobiliary disorders

SOC hepato-biliary disorders:

The proportion of subjects in the etrasimod 2 mg group experiencing TEAEs in the Hepatobiliary disorders SOC was similar between the Pivotal UC Pool and the All Indications Pool and greater in the etrasimod 2 mg group compared to placebo in both pools (2.1% vs 0.4% on placebo and 2.2% vs 0.8%). TEAEs reported in by ≥ 2 subjects on etrasimod 2 mg (none reported on placebo) were Liver disorder, Cholestasis and Hepatic steatosis. Hepatic function abnormal and Liver injury were reported in All indications pool additionally.

SOC Investigations:

Relevant number of patients had increased levels of Alanine aminotransferase increased, Gamma-glutamyltransferase increased, Aspartate aminotransferase increased, Blood alkaline phosphatase increased, bilirubin increased, Transaminase increased, Hepatic enzyme increased, etc. on etrasimod 2 mg. On placebo, mostly either no such events were reported, or in lower frequency.

SDEI: There were 2 subcategories of SDEI in the Liver-injury Category: Liver transaminases elevation and Bilirubin elevation.

Subjects with liver injury were identified by having a TEAE PT of interest accompanied by any liver transaminase elevation > 5 × ULN or a sustained elevation > 3 × ULN and/or bilirubin elevation > 2 × ULN without Gilbert's syndrome.

The proportion of subjects in the etrasimod 2 mg group with SDEI was similar in both the Pivotal UC and All Indications Pools and was higher than on placebo (pivotal UC pool: 1.3% vs 0.8%, all indications pool: 1% vs 0.08%); in both pools, the most frequently reported SDEI by PT (≥ 2 subjects in any treatment group) were ALT increased and AST increased.

Nervous system disorders

The proportion of patients with TEAEs in the Nervous system disorders SOC was greater in the etrasimod 2 mg group compared to the placebo group (etrasimod 2 mg: 64 subjects, 12.1%; placebo:

19 subjects, 7.3%) in the pivotal UC pool. Similar incidence was observed also in all indications pool on etrasimod (12.6%).

In the pivotal UC pool, TEAE PTs reported by ≥2 subjects in the etrasimod 2 mg group were Headache, Dizziness, Migraine, Somnolence, and Head discomfort; of these, all TEAE PTs but Migraine had a greater frequency in the etrasimod 2 mg group compared to placebo.

Grade 3 TEAEs (both PT of Migraine) in the Nervous system disorders SOC were experienced by 2 subjects, both of which were in the etrasimod 2 mg group and both events were considered SAEs. All other subjects had Grade 1 or Grade 2 TEAEs.

TEAE PTs experienced by ≥2 subjects in the etrasimod 2 mg group All Indications Pool included those reported in the Pivotal UC Pool as well as the following: Paraesthesia, Sciatica, Taste disorder, Dizziness postural, Hypoaesthesia, Presyncope, Tension headache, Transient ischaemic attack.

All additional TEAE PTs in the All Indications Pool were single TEAE PTs and included Memory impairment, Speech impairment, Tremor, and Vascular encephalopathy.

Grade 3 TEAEs were experienced by 1 subject (Non-UC) not included in the Pivotal UC Pool with a TEAE PT of Neuropathy peripheral (non-SAE, not related, dose not changed, resolving); the remaining events not reported in the Pivotal UC Pool were Grade 1 and Grade 2 TEAEs.

SDEI: Posterior reversible encephalopathy syndrome (PRES) was considered an SDEI and included PTs of Leukoencephalopathy, Toxic leukoencephalopathy, Autoimmune encephalopathy, and Immune effector cell-associated neurotoxicity syndrome. There were no SDEI of PRES in any etrasimod clinical study.

With the updated information, overall frequency of the events under this SOC did not change relevantly.

SAEs

In the PC UC pool 3 SAEs were reported on etrasimod (0.6%, EAIR 0.01), none on placebo: PTs of Migraine in 2 subjects [study APD334-301], Intracranial pressure increased [study APD334-301].

In the All UC pool 7 SAEs on etrasimod (none on placebo) were as follows: migraine, transient ischaemic attack (2 each), fine motor skill dysfunction, intracranial pressure increased, and demyelination (1 each).

Non-SAE events cerebral small vessel ischaemic disease, ocular migraine and Vascular encephalopathy were reported as ongoing events.

None of the events was considered drug-related by the applicant, but both cases of SAEs migraine represent worsening of the condition from the medical history and potential causal relationship is considered possible.

Psychiatric disorders

In the PC UC Pool 13 (2.3 %, EAIR [0.05]) participants in the etrasimod 2 mg group experienced TEAEs coding to PTs in the Psychiatric disorders SOC, compared with 4 (1.3%, EAIR [0.03]) participants in the placebo group.

The TEAEs most frequently reported by participants in the etrasimod 2 mg group were anxiety (3; 0.5%; EAIR [0.01]), insomnia (3; 0.5%; EAIR [0.01]), and depression (2; 0.3%, EAIR [<0.01]). The remaining events (agitation, attention deficit hyperactivity disorder, initial insomnia, mental disorder and sleep disorder) were each reported in 1 participant (0.2%, EAIR [<0.01]).

In the placebo group, the events insomnia and depression were reported in 2 participants each (0.6%, EAIR [0.02]). The remaining event, panic attack, was reported in 1 participant (0.3%, EAIR [<0.01]).

In the All indication pool: The TEAEs most frequently reported by participants in the etrasimod 2 mg group were anxiety, insomnia (5 each; 0.5%; EAIR [<0.01]), depression (4; 0.4%, EAIR [<0.01]), and initial insomnia (2; 0.2%, EAIR [<0.01]). The remaining events (agitation, alcoholism, attention deficit hyperactivity disorder, bipolar disorder, confusional state, irritability, mental disorder, panic attack, sleep disorder, and suicidal ideation) were each reported in 1 participant (<0.1%, EAIR [<0.01]). In the updated All Indications Pool additional participants reported the following events: anxiety (5), depression, insomnia (4 each), bipolar disorder (2), abnormal dreams, confusional state, irritability, libido decreased, mental disorder, and restlessness (1 each). In the placebo group, no events additional to those reported in the PC UC Pool were reported in the All Indications Pool.

TEAEs of thrombosis, embolism, haemorrhage, coagulation

Number of events related to thrombosis and embolism was very low and did not show any pattern.

In the PC UC pool, a total of 17 (2.95%) participants in the etrasimod 2 mg dose group (N = 577) and 2 (3.85%) participants in the etrasimod < 2 mg group (N = 52) experienced any TEAEs based on haemorrhage terms (lab-related terms and non-lab/clinical events) (EAIR 0.06 and 0.17 respectively) compared with 7 (2.23%) of participants in the placebo group (N = 314, EAIR 0.06).

In the updated All UC Pool, a total of 50 (4.82%) participants in the etrasimod 2 mg group (N = 1037) and 2 (3.85%) participants in the etrasimod 1 mg group (N = 52) experienced any treatment emergent haemorrhage event (lab terms or non-lab terms). EAIRs were 0.05 for the etrasimod 2 mg group and 0.17 for the 1 mg group, respectively. In the placebo group (N = 322) 7 (2.17%) participants experienced any haemorrhage event (EAIR 0.06).

In the updated All Indications Pool, 56 (4.41%, EAIR 0.05) participants in the etrasimod 2 mg group, 4 (4.04%, EAIR 0.16) participants in the etrasimod <2 mg group and 3 (4.05%, EAIR 0.13) participants in the etrasimod >2 mg group experienced any treatment-emergent haemorrhage event (lab term or non-lab term). As a laboratory term, additionally one new event of Coagulopathy was reported in the updated All Indications Pool that was not previously reported in the updated All UC Pool.

Overall, majority of the events occurred in single patients and was unique term. From the clinical terms rectal haemorrhage (5 participants, 0.48%), haematochezia (4 participants, 0.39%), contusion (4 participants, 0.39%) and epistaxis (4 participants, 0.39%) were among the most frequently reported events.

Across all pools, a majority of events were reported in unique participants and for most cases, there were no abnormalities in coagulation parameters or platelets reported at the time of the event and no clear pattern or trends for coagulation parameters in these participants. Similar observations were noted for clinical haemorrhage events in the PC UC Pool and All Indications Pool. A majority of the events across all pools were mild or moderate in severity; 4 SAEs were reported in the All UC Pool (Cystitis haemorrhagic, Gastrointestinal haemorrhage, Rectal haemorrhage, and Haematochezia). None of these events had associated abnormalities in clotting parameters or platelets and none of these SAEs were attributed to study treatment by the investigator or the applicant.

Neoplasms Benign, Malignant and Unspecified

In the Pivotal UC Pool, 2 subjects in the etrasimod 2 mg group had Colon adenoma and Papilloma (verbatim term: Eyelid papilloma). No subjects in the placebo group had TEAEs in this SOC.

In all indications pool, of the events not previously reported in the Pivotal UC Pool, Haemangioma of liver (in 2 patients), Neuroendocrine tumour, Haemangioma of bone, Malignant melanoma, Pituitary

tumour benign, Seborrhoeic keratosis, Squamous cell carcinoma of skin (in 1 patient each) were experienced by 8 subjects in the etrasimod 2 mg treatment group.

From the 3 cases of haemangioma reported in the etrasimod UC studies, 1 participant presented with symptoms of back pain which led to the diagnosis of haemangioma in the spine. Neither participant with hepatic haemangioma reported clinical symptoms in conjunction with the events. For 1 participant, hepatic haemangioma was detected incidentally on routine clinical examination with ultrasound. For the second participant, it was detected incidentally on ultrasound during the investigation of elevated hepatic enzymes. All 3 events were assessed as unrelated to study treatment by the investigator. All 3 participants continued in the study, with no dose adjustments in study drug as a consequence of the events.

SDEI: TEAEs for the Malignancies Category were identified based upon a PT.

Three subjects had PTs in the Malignancies Category (0.3%, EAIR < 0.01) in the etrasimod 2 mg group (PTs of Malignant melanoma, Neuroendocrine tumour, and Squamous cell carcinoma of skin), 1 subject (0.3%, EAIR < 0.01) in the placebo group (PT of Squamous cell carcinoma of skin), and no subjects in the etrasimod < 2 mg or etrasimod > 2 mg groups:

APD334-303 one Subject with UC in his 30's had a fatal SAE of Neuroendocrine tumour beginning on Study Day 196 of Study APD334-303 (etrasimod 2 mg; subject received placebo in Study APD334-301) that was considered an SDEI in the Malignancies Category.

APD334-303 one Subject with UC in her 30's had an SDEI of Malignant melanoma. The verbatim reported term was "Melanocytic mole manifestation,"; this event was not confirmed as a malignancy. Coding of the reported term will be updated in the clinical database.

APD334-201 one Subject with AD in his 60's had 3 SDEI of Squamous cell carcinoma of skin during participation in both the placebo-controlled and open-label periods of Study APD334-201. The subject did not have a history of skin cancer. The subject received placebo during the blinded placebo-controlled period and received etrasimod 2 mg during the open-label period. The first SDEI (Grade 2, dose not changed, not related, resolved) began on Study Day 31 while the subject was receiving placebo. The second and third events were reported on Study Day 338 and included a Squamous cell carcinoma of skin on the subject's nose bridge (Grade 1, dose not changed, not related, resolved) and a Squamous cell carcinoma of skin (Grade 2, dose not changed, not related, resolved) on the back of the subject's scalp.

Subgroup analyses of TEAEs:

Subgroup analysis of TEAEs based on sex, race, ethnicity and region did not show any apparent major differences in the TEAE profile.

Summary of the Incidence of Infections in Participants with Lymphopenia or Neutropenia

Incidence of the TEAEs related to infections was evaluated in the subgroups of patients with various Grades of lymphopenia and neutropenia (see the definitions of the Grades in the section on "laboratory findings"). There was no difference seen in the frequency of infections in the patients with Grade 2 lymphopenia across the treatment. Higher frequencies were reported for those with Grade 3 and 4 lymphopenia on etrasimod (11%, EAIR: 0.152 and 18.8%, EAIR: 0.270, respectively in Study APD334-301) compared to placebo (none). Numbers of patients with high-degree neutropenia were low.

Severe, Opportunistic or Serious Infections and Lymphopenia or Neutropenia

Overall, a total of 6 participants with Grade 2 lymphopenia (4 in the etrasimod 2 mg group and 2 in the placebo group) experienced an infection in any category; A total of 2 participants with Grade 3 lymphopenia in the etrasimod 2 mg group experienced a severe (1 participant) or serious infection (1

participant); A total of 2 participants with Grade 2 neutropenia in the etrasimod 2 mg group (none in placebo) who experienced had a severe (1 participant) or serious infection (1 participant). No participants with Grade 3 neutropenia, or Grade 4 neutropenia or lymphopenia experienced any infections in the categories of severe, opportunistic or serious infections in studies (Studies APD334-301, APD334-302, or APD334-003) or in the pooled analysis (Studies APD334-302 and APD334-003).

Additional Analyses for Long Term Safety and Infections

Subgroup analysis of the TEAEs per time to onset showed that the EAIRs for any TEAEs, including infections TEAEs were higher in exposure time up to 24 weeks than those reported for exposures >24 weeks and >52 weeks. After 24 weeks, the safety profile and pattern of TEAEs, SAEs, TEAEs leading to discontinuation, and SDEIs for exposures of >24 weeks and >52 weeks was overall similar. A similar finding was observed for the elderly population analysis, that is, the safety profile of etrasimod with regard to infections was similar for exposure > 24 weeks and > 52 weeks.

Events of infections did not occur more frequently after 52 weeks treatment. The EAIR for herpes infections did not increase with exposure > 52 weeks. The EAIR for events of lymphopenia was slightly higher for > 52 weeks compared with up to 52 weeks of exposure (EAIR 0.14 vs EAIR 0.08).

2.6.8.2. Serious adverse event/deaths/other significant events

One **death** was reported in the etrasimod clinical development program (from Phase 3 OLE Study APD334-303).

A subject in the 30-year age range with UC, received placebo in Study APD334 301 until Day 97, then received etrasimod 2 mg in Study APD334-303 (OLE) up to Study Day 170 (discontinued due to lack of efficacy). In Study APD334-301, the subject had a Grade 3 SAE of Cellulitis on Day 44 that resolved on Day 55 and was assessed as probably related to study treatment by the Investigator. In Study APD334-303, the subject had a Grade 3 SAE of Colitis ulcerative (described as aggravated ulcerative colitis) on Day 151, which was resolved on Day 157 and was assessed as unlikely related to study treatment by the Investigator. On Day 196, an SAE of Neuroendocrine tumour of unknown primary origin was reported. The subject died on Day 212 with cause of death attributed to the event of Neuroendocrine tumour. The SAE of Neuroendocrine tumour was assessed as unlikely related to study treatment by the Investigator and the Sponsor.

Other SAEs:

The proportion of subjects experiencing at least 1 SAE was similar across etrasimod 2 mg and placebo groups (n=26 [4.5 %] vs 17 [5.4%] on placebo) in the Placebo-Controlled UC pool.

The greatest proportion of subjects (≥ 2%) reported SAEs in the SOC Gastrointestinal disorders; the most frequently reported TEAE was Colitis ulcerative for the 3 UC pools and the All Indications Pool.

Most SAEs by PT were reported for a single subject in 1 or more treatment groups by pool. Across all ISS studies, 16 subjects experienced more than 1 SAE.

SAEs that led to permanent study treatment discontinuation included 3 subjects each in the etrasimod 2 mg (PT Colitis Ulcerative) and etrasimod < 2 mg (PTs Colitis Ulcerative, Anal abscess) groups and 2 subjects in the placebo group (PTs Large intestine perforation, Abdominal pain upper).

Five subjects total across all treatment groups had TEAEs leading to study treatment interruption that were SAEs (etrasimod 2 mg: 3 subjects; etrasimod < 2 mg: no subjects; placebo: 2 subjects); the PTs in the etrasimod 2 mg group were Intracranial pressure increased (1 subject) and Migraine (2 subjects).

The most frequent SAEs by PT (ie, in ≥ 2 subjects in any treatment group) were Colitis ulcerative, Migraine, and Anaemia (no subjects had SAEs of Migraine in the placebo group).

Table 56: Serious Adverse Events by System Organ Class and Preferred Term (Placebo-Controlled UC Pool)

System Organ Class Preferred Term	Etrasimod 2 mg/day (N=577) n (%) [EAIR]	Etrasimod < 2 mg/day (N=52) n (%) [EAIR]	Etrasimod Any Dose (N=629) n (%) [EAIR]	Placebo (N=314) n (%) [EAIR]
Subjects with at Least 1 Serious TEAE	26 (4.5) [0.09]	3 (5.8) [0.25]	29 (4.6) [0.10]	17 (5.4) [0.15]
Gastrointestinal Disorders	12 (2.1) [0.04]	2 (3.8) [0.17]	14 (2.2) [0.05]	10 (3.2) [0.09]
Colitis ulcerative	9 (1.6) [0.03]	2 (3.8) [0.17]	11 (1.7) [0.04]	6 (1.9) [0.05]
Abdominal pain	1 (0.2) [< 0.01]	0	1 (0.2) [< 0.01]	1 (0.3) [< 0.01]
Mucosal prolapse syndrome	1 (0.2) [< 0.01]	0	1 (0.2) [< 0.01]	0
Proctitis	1 (0.2) [< 0.01]	0	1 (0.2) [< 0.01]	0
Abdominal pain upper	0	0	0	1 (0.3) [< 0.01]
Duodenal ulcer perforation	0	0	0	1 (0.3) [< 0.01]
Large intestine perforation	0	0	0	1 (0.3) [< 0.01]
Infections and Infestations	3 (0.5) [0.01]	1 (1.9) [0.08]	4 (0.6) [0.01]	5 (1.6) [0.04]
COVID-19	1 (0.2) [< 0.01]	0	1 (0.2) [< 0.01]	1 (0.3) [< 0.01]
COVID-19 pneumonia	1 (0.2) [< 0.01]	0	1 (0.2) [< 0.01]	1 (0.3) [< 0.01]
Pneumonia bacterial	1 (0.2) [< 0.01]	0	1 (0.2) [< 0.01]	0
Anal abscess	0	1 (1.9) [0.08]	1 (0.2) [< 0.01]	0
Campylobacter infection	0	0	0	1 (0.3) [< 0.01]
Cellulitis	0	0	0	1 (0.3) [< 0.01]
Peritonitis	0	0	0	1 (0.3) [< 0.01]
Nervous System Disorders	3 (0.5) [0.01]	0	3 (0.5) [0.01]	0
Migraine	2 (0.3) [< 0.01]	0	2 (0.3) [< 0.01]	0
Intracranial pressure increased	1 (0.2) [< 0.01]	0	1 (0.2) [< 0.01]	0
Blood and Lymphatic System Disorders	2 (0.3) [< 0.01]	0	2 (0.3) [< 0.01]	2 (0.6) [0.02]
Anaemia	2 (0.3) [< 0.01]	0	2 (0.3) [< 0.01]	2 (0.6) [0.02]
Musculoskeletal and Connective Tissue Disorders	2 (0.3) [< 0.01]	0	2 (0.3) [< 0.01]	0
Arthralgia	1 (0.2) [< 0.01]	0	1 (0.2) [< 0.01]	0
Musculoskeletal chest pain	1 (0.2) [< 0.01]	0	1 (0.2) [< 0.01]	0
Cardiac Disorders	1 (0.2) [< 0.01]	0	1 (0.2) [< 0.01]	0
Coronary artery disease	1 (0.2) [< 0.01]	0	1 (0.2) [< 0.01]	0
Immune System Disorders	1 (0.2) [< 0.01]	0	1 (0.2) [< 0.01]	0
Allergy to arthropod bite	1 (0.2) [< 0.01]	0	1 (0.2) [< 0.01]	0
Injury, Poisoning and Procedural Complications	1 (0.2) [< 0.01]	0	1 (0.2) [< 0.01]	0
Hepatobiliary Procedural Complication	1 (0.2) [< 0.01]	0	1 (0.2) [< 0.01]	0

System Organ Class Preferred Term	Etrasimod 2 mg/day (N=577) n (%) [EAIR]	Etrasimod < 2 mg/day (N=52) n (%) [EAIR]	Etrasimod Any Dose (N=629) n (%) [EAIR]	Placebo (N=314) n (%) [EAIR]
Investigations	1 (0.2) [< 0.01]	0	1 (0.2) [< 0.01]	0
Hepatic enzyme increased	1 (0.2) [< 0.01]	0	1 (0.2) [< 0.01]	0
Pregnancy, Puerperium and Perinatal Conditions	1 (0.2) [< 0.01]	0	1 (0.2) [< 0.01]	0
Anembryonic gestation	1 (0.2) [< 0.01]	0	1 (0.2) [< 0.01]	0
Surgical and Medical Procedures	1 (0.2) [< 0.01]	0	1 (0.2) [< 0.01]	0
Breast conserving surgery	1 (0.2) [< 0.01]	0	1 (0.2) [< 0.01]	0
Hepatobiliary Disorders	0	0	0	1 (0.3) [< 0.01]
Jaundice	0	0	0	1 (0.3) [< 0.01]
Renal and Urinary Disorders	0	0	0	1 (0.3) [< 0.01]
Hydronephrosis	0	0	0	1 (0.3) [< 0.01]

1. TEAE is defined as AE that started after the first dose of study treatment. TEAE is associated with the treatment most recently received by the subject at the time of onset. Terms are coded using MedDRA v24.1.
2. EAIR is defined as the number of subjects with AE divided by the total subject-years at risk for AE (sum of individual time to first episode of AE, or time in the study if subject was event-free). EAIR is presented per 1 subject-years
3. Adverse events are sorted by decreasing frequency of SOC, and within SOC, by decreasing frequency of preferred term, in the etrasimod 2 mg/day treatment group.
4. Subjects are counted only once per summarisation level per treatment group.
5. Percentages are based on the number of subjects in the pool.
6. Source: ISS Table 14.3.1.4.2

The All UC Pool, with a subset of participants exposed to > 52 weeks of etrasimod 2 mg, had a somewhat higher proportion of subjects experiencing SAEs in the etrasimod 2 mg group (n=67; 7.1% of subjects) compared to those treated with etrasimod < 2 mg or placebo (n=17; 5.3%).

Most SAEs according to PT occurred in 1 subject. The following unique reports of SAEs on etrasimod 2 mg that were not previously reported in the Placebo-Controlled UC Pool or Pivotal UC Pool are: Colitis, haematochezia, pancreatitis, proctitis ulcerative, appendicitis, chronic sinusitis, herpes simplex meningitis, pneumonia, pyelonephritis acute, fine motor skill dysfunction, atrial fibrillation, atrioventricular block second degree, back pain, abortion spontaneous, uncoded events (disturbance of consciousness, worsening of depression), adrenal insufficiency, fatigue, accident, neuroendocrine tumour (fatal case), cystitis haemorrhagic, deep vein thrombosis (each reported in 1 patients), gastroenteritis, transient ischaemic attack (each reported in 2 patients), and iron deficiency anaemia (reported in 3 patients). None of these PTs were reported on placebo.

As in the placebo-controlled pool, the SOC that included the highest number of subjects with SAEs was Gastrointestinal Disorders; the most frequently reported SAE was PT Colitis ulcerative (n=25; 2.7%).

Thirteen additional subjects had SAEs that led to permanent study treatment discontinuation and were not previously reported in the Placebo-Controlled UC Pool. All of these were in the etrasimod 2 mg group (16 subjects in total); these SAE PTs were Atrial fibrillation, Colitis ulcerative, Herpes simplex meningitis, Transient ischaemic attack, and Atrioventricular block second degree (Mobitz Type I).

Five subjects had SAEs that led to study treatment interruption and were not previously reported in the Placebo-Controlled UC Pool, all of which were in the etrasimod 2 mg group; these SAE PTs were Colitis ulcerative, Pancreatitis, COVID-19, and Appendicitis.

SAEs of Iron deficiency anaemia, Gastroenteritis, and Transient ischaemic attack were experienced by ≥ 2 subjects in any treatment group and were not previously described in the Placebo-Controlled UC Pool or Pivotal UC Pool.

Updated All UC pool:

The proportion of subjects in the etrasimod 2 mg group who experienced at least 1 SAE in the updated All UC Pool was 9.1% compared to 7.1% of subjects in the initial All UC Pool, however, the EAIR was the same in both the initial and updated All UC Pool (EAIR 0.09). In total, there were 27 additional subjects in the etrasimod 2 mg group with at least 1 SAE in the updated All UC Pool compared to the initial All UC Pool.

In the updated All UC Pool, the most frequently reported SAEs by PT (≥ 2 subjects) in the etrasimod 2 mg group were Colitis ulcerative, COVID-19, COVID-19 pneumonia, Gastroenteritis, Migraine, Transient ischaemic attack, Anaemia, Iron deficiency anaemia, and Back pain. The EAIR for these most frequently reported SAEs by PT was the same in both the updated and initial pools.

Other Pools: Serious Adverse Events

SAEs related to TEAEs of interest that occurred in only 1 subject in one or more treatment groups and not previously described in the All UC Pool (and therefore derived from the Non-UC Pool) included 4 unique SAEs in the Infections and Infestations SOC (Extradural abscess, Sepsis, Staphylococcal bacteraemia, Tooth abscess) and 1 SAE each in the Pregnancy, Puerperium, and Perinatal Conditions SOC (Ectopic pregnancy) and Respiratory, Thoracic and Mediastinal Disorders SOC (Chronic obstructive pulmonary disease). In total, there were 29 additional subjects in the etrasimod 2 mg group with at least 1 SAE in the updated All Indications Pool compared to the initial All Indications Pool. These largely overlapped with the additional events in the updated All UC pool.

No additional subjects had SAEs leading to study treatment interruption in the Non-UC Pool and all indications pool, respectively.

2.6.8.3. TEAEs in the Clinical Pharmacology Pool

Overall proportion of patients with TEAEs was higher on etrasimod than on placebo and showed dose-dependency: 17.9% on 2 mg, 16.6% on < 2 mg; 36.7% on >2 mg vs 6.8% on placebo. Overall, 0.7% of subjects had SAEs on etrasimod 2 mg, but none were reported on other dose of etrasimod or on placebo.

TEAEs leading to discontinuation were reported in 2.3% of subjects on etrasimod 2 mg.

TEAE profile on etrasimod 2 mg was roughly similar to that of patients population with headache, dizziness, somnolence, presyncope, diarrhoea, nausea, constipation, vomiting, dermatitis contact, skin irritation, pruritus, medical site and catheter site reactions, fatigue, AST and ALT increased, sinus bradycardia, AV blocks first and second degrees, and arthropod bite occurring in >2 patients. Events with higher incidence on etrasimod 2 mg than on placebo were those reported as ADRs: bradycardia, AV blocks, AST and ALT increased. No dose-dependency was apparent for TEAEs.

Cases of QT prolongation, QRS prolongation, abnormal T wave, sinus arrest, ventricular extrasystoles, supraventricular extrasystoles and ventricular tachycardia (on >2 mg etrasimod) were reported.

Related TEAEs with higher frequency on etrasimod 2 mg than on placebo (>=1%) were: dizziness, headache, somnolence, nausea, vomiting, sinus bradycardia, AV block I degree, AST and ALT increased.

2.6.8.4. Laboratory findings

Clinical Chemistry

Treatment with etrasimod 2 mg was associated with changes in liver chemistry (ALT, AST, ALP, total bilirubin and gammaGT) values and total cholesterol (non-fasted) parameters. At any time on treatment with etrasimod 2 mg ALT, AST, total bilirubin, ALP and GGT were above normal range in 35%, 25%, 8.5%, 18.2% and 28.6% of patients vs. 15%, 9.2%, 4.1%, 12.7% and 11.1% of those on placebo (Placebo-controlled UC pool).

- No subjects had liver chemistry elevations that met Hy's Law criteria in any treatment group in any pool.
- Across pools, sporadic, transient elevations in liver enzymes were observed, these were generally < 3× ULN and asymptomatic with no clinically meaningful trends observed.
- In all pools, AST and/or ALT elevations > 3 × ULN were more frequent in the etrasimod 2 mg group compared to the placebo group (4.4% vs. 1.5%, respectively), but elevations > 5 × or 10 × ULN were similar in both treatment groups.
- In all pools, elevations in GGT, including elevations > 5 × ULN were more frequent in the etrasimod 2 mg group than the placebo group.
- In the UC pools, median total cholesterol (non-fasted) in the etrasimod 2 mg group increased from Baseline beginning at Week 2 and the increase continued through Week 52. There were no remarkable changes in serum triglycerides.
  - In the Pivotal UC Pool, the median change from Baseline in total cholesterol (non-fasted) at Week 2: etrasimod 2 mg, 0.230 mmol/L (range: −3.09, 2.20) and placebo, 0.110 mmol/L (range: −2.02, 2.25) and at Week 52: etrasimod 2 mg, 0.490 mmol/L (range: −2.26, 3.26) and placebo, 0.115 mmol/L (range: −2.31, 2.31] in placebo). Median values remained within the normal range.

Haematology and TBNK

- There were no clinically significant changes observed for haematocrit and haemoglobin concentrations and erythrocyte, basophil, eosinophil, monocyte and platelet counts in the etrasimod 2 mg group across all pools.
- Lymphocyte count decreased in the etrasimod 2 mg group across pools, which was generally observed at Week 2. Median lymphocyte counts were similar at Weeks 2 and 52 (little to no further decreases with longer exposures). No subjects had SAEs that were associated with decreased lymphocyte counts.
  - For the etrasimod 2 mg group in the Pivotal UC Pool, decreases in lymphocyte count from baseline (i.e., Median 1.640 × 10^9 cells/L; range: 0.39 to 7.07 × 10^9 cells/L) were observed by Week 2 (median change from Baseline to Week 2: −0.840 × 10^9 cells/L (range: −4.75 × 10^9, 2.77 × 10^9). The median change from Baseline to Week 52 was −0.930 × 10^9 cells/L (range: −3.73 × 10^9, 0.82 × 10^9 cells/L).
  - In the Pivotal UC Pool, 6 subjects (1.2%) had lymphocyte counts < 0.2 × 10^9 cells/L at the last on-treatment visit and 18 subjects (3.5%) had lymphocyte counts in this range at any time post-Baseline. Lymphocyte counts < 0.5 × 10^9 cells/L were observed in 117 subjects (22.9%) at the last on-treatment visit and 206 subjects (39.7%) at any time post-Baseline.

- No subjects with ALC < 0.2 × 10^9 cells/L subsequently reported an SDEI in the Severe or Opportunistic Infections Category in the Pivotal UC Pool or the All Indications Pool.
- In subjects who discontinued etrasimod therapy for any reason and returned for off-treatment follow-up, lymphocyte counts were in the normal range for 87.9% of subjects in the All Indications Pool within 2 weeks after stopping treatment. However, number of patients was very low.

- In the Pivotal UC Pool, decreases in neutrophil count from baseline (i.e., 4.455 × 10^9 cells/L; range: 1.05, 19.93) were observed in the etrasimod 2 mg group by Week 2 (median change from Baseline at Week 2: −0.595 × 10^9 cells/L [range: −10.98 × 10^9, 9.13 × 10^9] and remained by Week 16 (etrasimod 2 mg: −1.120 × 10^9 cells/L [range: −10.33, 5.94] vs. placebo: 0.080 × 10^9 cells/L [range: −6.13, 2.46]); ie, there were no further decreases in neutrophil count through Week 52. Median change from Baseline to Week 52 was −0.870 × 10^9 cells/L (range: −11.36 × 10^9, 4.34 × 10^9). Analyses (placebo-controlled UC pool) conducted to evaluate shift from baseline to last on-treatment value of neutrophils across the 3 categories "low", "normal" and "high", showed that proportion of the patients with neutrophil counts below normal increased on treatment with etrasimod 2 mg to 8.9% from 2% at baseline, whereas 3.3% on treatment vs. 4.6% at baseline was observed on placebo.
- Decreases in leukocyte count over time were primarily driven by decreases in lymphocyte counts.

Follow-up information is available for only a fraction of treated population. Observed changes in haematological parameters returned to baseline levels at week 2 in follow-up in these patients.

Changes in selected haematology parameters and TBNK cells are presented in the tables below.

Table 57: Changes in selected haematology parameters (Pivotal UC pool)

		Baseline (median) NEtr=526 Npla=259	Week 2 (median change) NEtr=478 Npla=234	Week 16 (median change) NEtr=201 Npla=79	Week 52 (median change) NEtr=157 Npla=40	Follow-up Week 2 (median change) NEtr=36 Npla=6
Neutrophils × 10^9 cells/L	Etr	4.455	-0.595	-1.120	-0.870	-0.480
	Pla	4.570	-0.190	-0.080	-0.150	3.530
Monocytes × 10^9 cells/L	Etr	0.455	0.020	-0.010	-0.050	-0.035
	Pla	0.450	0.000	0.020	0.010	0.145
Lymphocytes × 10^9 cells/L	Etr	1.640	-0.840	-0.878	-0.930	0.020
	Pla	1.620	0.100	0.130	0.055	-0.325

Platelets × 10^9 cells/L	Etr	315.00	-2.0	-28.50	-22.00	18.00
	Pla	294.00	2.0	-10.50	-17.00	61.00
TBNK cells						
CD3+ T cell cell/μL	Etr	1242.0	-670.0	-755.0	-804.0	-2.0
	Pla	1200.0	42.0	28.0	-15.5	-249.5
CD3+CD4+ T cell cell/μL	Etr	717.0	-490.0	-547.0	-556.0	-45.0
	Pla	695.0	17.0	29.0	-19.0	-90.0
CD3+CD8+T cell cell/μL	Etr	435.0	-150.0	-185.0	-214.0	5.0
	Pla	448.0	24.0	9.0	1.5	-135.0
CD3-CD19+B cell cell/μL	Etr	172.0	-130.0	-141.0	-130.0	9.0
	Pla	170.0	-1.0	4.0	16.0	7.5
CD56+CD16+ NK cell cell/μL	Etr	166.0	12.0	22.0	21.0	24.0
	Pla	156.0	16.5	27.5	25.5	4.5
CD14+ monocyte cell/μL	Etr	483.0	-16.0	-75.0	-65.0	-61.0
	Pla	462.0	6.5	-2.0	-30.0	38.5

Table 58: Incidence of markedly abnormal counts of lymphocytes, neutrophils and CD4 (Placebo-controlled UC pool; Last on-treatment)

	Etrasimod 2 mg/day (N=577) **n (%)**	**Etrasimod 1 mg/day (N=52)** **n (%)**	**Placebo (N=314)** **n (%)**
Last on-treatment			
Lymphocytes (10^9/L)	561	52	304
<0.2 x 10^9/L	6 (1.1)	1 (1.9)	0
<0.5 x 10^9/L	125 (22.3)	5 (9.6)	1 (0.3)
Neutrophils (10^9/L)	561	52	304
<0.5 x 10^9/L	0	0	0
<1.0 x 10^9/L	3 (0.5)	0	2 (0.7)
CD3+CD4+ABS (cells/uL)	511	0	250
<50 cells/uL	58 (11.4)	0	0
<200 cells/uL	343 (67.1)	0	2 (0.8)
Any time post-baseline			
Lymphocytes (10^9/L)	**568**	**52**	**307**
<0.2 x 10^9/L	18 (3.2)	2 (3.8)	0
<0.5 x 10^9/L	215 (37.9)	10 (19.2)	5 (1.6)
Neutrophils (10^9/L)	568	52	307
<0.5 x 10^9/L	1 (0.2)	0	0
<1.0 x 10^9/L	9 (1.6)	0	4 (1.3)
CD3+CD4+ABS (cells/uL)	518	0	254
<50 cells/uL	80 (15.4)	0	0
<200 cells/uL	418 (80.7)	0	10 (3.9)

Etrasimod induced decrease in T and B cells, while leaving NK and monocytes unaltered in circulation, as assessed in the Pivotal UC Pool only.

- T cells (total, CD4+, and CD8+) and B cells (CD19+) were reduced with etrasimod but not placebo starting at Week 2 and remained reduced through Week 52.
- Reductions in ALC were predominantly driven by reductions in CD4+ T cells and CD19+ B cells, which were reduced to a greater magnitude than CD8+ T cells.
- T and B cells returned to near-baseline levels by the 2- and 4-Week Follow-up visits (ie, off-treatment visits).

- NK cell counts (CD56+CD16+) and absolute monocytes (CD14+) were not significantly changed at any timepoint in both etrasimod and placebo treatment groups.
- Relative frequencies of NK, monocytes, and CD8+ T cells increased in the etrasimod group beginning at Week 2, was maintained through Week 52, and returned to near baseline by the 2-Week Follow-up visit.

Subgroup analysis:

Subgroup analysis of patients with various grades of lymphopenia and neutropenia (Defined as per CTCAE version 5: Grade 2 lymphopenia = ALC of 0.5 to <0.8 x 109 cells/L; Grade 3 lymphopenia = ALC of 0.2 to <0.5 x 109 cells/L; Grade 4 lymphopenia = ALC of <0.2 x 109 cells/L and Grade 2 neutropenia = ANC of 1.0 to <1.5 x 109 cells/L; Grade 3 neutropenia = ANC of 0.5 to <1.0 x 109 cells/L; Grade 4 neutropenia = ANC of <0.5 x 109 cells/L) showed higher frequency of lymphopenia of all Grades on etrasimod compared to placebo (Grade 2: 64%-75.4% vs 8.4%-14.6%, Grade 3: 28.5%-43.9% vs. 1.3%-2.1%; Grade 4: 0.6%-5.5% vs. 0%, respectively). Depending on the data set evaluated (Study APD334-301 or pooled APD334-302 and APD334-003), high-grade (Grades 3 and 4) lymphopenia was observed in up-to 44% of the etrasimod-treated population.

Lower absolute number of participants experienced neutropenia with lower difference to placebo of Grade 2 (4.7%-10.4% vs. 3.1%-7.6%, respectively). There was no difference seen in the frequencies of Grade 3 neutropenia across the treatments and only 1 subject had Grade 4 neutropenia on etrasimod (none on placebo).

Platelets

The reversible decrease in mean/median platelet counts observed in participants who received etrasimod 2 mg in the PC UC Pool was noted at Week 2 and stabilised by Week 16 of treatment. The decrease remained below 10%.

Coagulation parameters

Pooled analysis did not show any apparent changes in coagulation parameters in any of the pools.

Urinalysis

For all pools, there were no meaningful differences between etrasimod and placebo groups for the following parameters: Specimen appearance, colour, ketones, urine, protein, glucose, occult blood, microscopy, and nitrite parameters.

Vital signs

Heart Rate (HR)

In the Pivotal UC studies, subjects were monitored in the clinic for at least 4 hours upon treatment initiation (ie, first dose/Day 1 and as needed on Day 2) and for re initiation. At the end of the scheduled 4 hour, subjects who did not meet the protocol defined discharge criteria (HR ≥ 50 bpm or no more than 10 bpm lower than the pre dose (baseline) value, no evidence of second-degree AV block or higher, no cardiac symptoms such as, chest pain, dizziness, palpitations, light-headedness, shortness of breath, or syncope) were to undergo extended monitoring on Day 1 and second dose monitoring on Day 2.

During the 4-hour post-first dose monitoring period on Day 1, the greatest mean (SD) change by timepoint from predose HR in subjects in the Pivotal UC Pool occurred at Hour 3 (etrasimod 2 mg: -7.2 [8.98] bpm; placebo: 0.4 [7.93] bpm). Compared to Hour 3, the by-timepoint mean (SD) change from predose HR was smaller at Hour 4 (etrasimod 2 mg: -6.7 [8.58] bpm; placebo: 0.2 [7.85] bpm).

On Day 1 in the Pivotal UC Pool, the lowest HR attained by any subject in the etrasimod 2 mg group was 42 bpm, which occurred at Hour 3 postdose and was not accompanied by symptoms. HR recovered to 70 bpm at Hour 4; on Day 1, nadir HR was ≥ 50 bpm for ≥ 95% of subjects in the etrasimod 2 mg group.

The lowest HR attained by any etrasimod-treated subject in any pool was 35 bpm and occurred on Study Day 1 in UC Study APD334-003. A single, 0.5 mg dose of atropine for the event of Bradycardia, which was considered a Grade 2 TEAE, was administered and study treatment was interrupted. The subject's BP predose remained unchanged. The subject had a concurrent Grade 1 TEAE of Second-degree atrioventricular block (Mobitz Type I). Both TEAEs resolved without sequelae on Day 1. The subject was asymptomatic during both events and did not have any events of clinical consequence (eg, syncope, loss of consciousness). The subject completed 12 weeks of treatment without subsequent TEAEs in the Cardiac disorders SOC.

Mean (SD) changes in HR observed on Day 1 in the Pivotal UC Pool were not observed in the etrasimod 2 mg group at Week 2 (etrasimod 2 mg, -0.3 [9.63] bpm; placebo, 1.9 [9.41] bpm) or at Week 52 (etrasimod 2 mg: -0.3 [10.59] bpm; placebo: 0.3 [7.76] bpm).

About 33% of subjects developed HR below 60 bpm on Day 1 of etrasimod 2 mg treatment.

Table 59: Summary of Cardiac Effects on Vital Signs on Day 1 (Pivotal UC Pool)

	Result in Pivotal UC Pool	
Parameter Measured on Day 1	**Etrasimod 2 mg**	**Placebo**
Time to Day 1 nadir HR following dose (hours)		
n	526	260
Mean (SD)	2.49 (1.113)	2.18 (1.137)
Median (Min, Max)	2.08 (0.8, 9.9)	2.00 (0.8, 4.3)
Nominal hourly postdose timepoint with minimum heart rate observed, n (%)		
Hour 1	107 (20.3)	100 (38.5)
Hour 2	178 (33.8)	54 (20.8)
Hour 3	118 (22.4)	59 (22.7)
Hour 4	121 (23.0)	47 (18.1)
Incidence of subject's Day 1 nadir on Day 1 (n [%])[a]		
≥ 60 bpm	354 (67.2)	234 (90)
50 to 59 bpm	160 (30.3)	26 (10)
45 to 49 bpm	9 (1.7)	0
40 to 44 bpm	4 (0.8)	0
< 40 bpm	0	0

	Result in Pivotal UC Pool	
Parameter Measured on Day 1	**Etrasimod 2 mg**	**Placebo**
Subjects not meeting discharge criteria at Hour 4 postdose on Day 1 as determined by Investigator (n [%])	21 (4.0)	1 (0.4)

Percentages are based on the number of subjects in the pool unless specified otherwise.

Source: ISS Tables 14.3.14.1.1, 14.3.14.3.1, 14.3.14.4.1, 14.3.1.5.1, and 14.3.14.6.1

Subjects with HR < 50 bpm: Infrequent Symptoms and No Events of Clinical Consequence

In the Pivotal UC Pool, 13 (2.5%) subjects in the etrasimod 2 mg group had a post-baseline HR measurement < 50 bpm on Day 1. Of these 13 subjects, none had a drop in BP or required an intervention for the observed HR < 50 bpm on Day 1 and there were no events of clinical consequence (eg, syncope or loss of consciousness) in any subjects. However 4 subjects experienced cardiac TEAEs on Day 1. None of these events was considered an SAE.

Two subjects had an observed HR < 50 bpm with a decrease of ≥ 10 bpm (APD334-301, APD334-302) from predose HR.

TEAEs of Sinus bradycardia, or bradycardia and 1 TEAE of AV block were reported in these group. Majority of the patients had no symptoms. Only two patients had dizziness, or dizziness and palpitations.

Change in HR over time showed remained stable around 0 in median values and did not differ from placebo. However, maximum decrease in heart rate was larger on etrasimod 2 mg compared to placebo at all time points by more than 10 beats apart from week 40 measurements.

Mean Changes in Other Vital Signs on Day 1 and Over Time

Changes in systolic and diastolic BP on Day 1 in the Pivotal UC Pool were not considered clinically meaningful in either treatment group.

The greatest by-timepoint mean (SD) change from predose in systolic blood pressure was on etrasimod 2 mg, -2.2 (10.00) mmHg at Hour 2 postdose and on placebo, -2.1 (8.92) mmHg at Hour 1 postdose.

The greatest by-timepoint mean (SD) change from predose in diastolic blood pressure was: etrasimod 2 mg, -3.9 (8.04) mmHg at Hour 2 postdose; placebo, -1.6 (7.32) mmHg at Hour 3 postdose.

Up to Week 52 in the Pivotal UC Pool, mean changes from predose in both systolic and diastolic BP were ≤ 3.6 mmHg in the etrasimod 2 mg group, compared to ≤ 1.4 mmHg in the placebo group. Median change remained at 2 mmHg for systolic and 0-1 mmHg for diastolic BP, with placebo at 0. Change in maximum value of systolic BP was larger on etrasimod at all timepoints (i.e. increase in BP) compared to placebo. No clear difference in these values and vs. placebo was observed for diastolic BP.

There were no clinically meaningful changes in respiratory rate, body temperature or weight in any treatment group in any pool.

Electrocardiogram

On Day 1 of treatment, number of patients with abnormal clinically relevant ECGs increased from 56 (10%) to 69 (12.3%) on etrasimod 2 mg, but did not change relevantly on placebo (30 patients [9.9%] at baseline vs. 28 patients [9.2%] on placebo treatment). On day 2 in total 16 patients on etrasimod and 1 patient on placebo required extended ECG monitoring. From these, 5 patients had

abnormal clinically relevant ECG, all had received etrasimod 2 mg/day (31.3%). ECG of 3 of these patients normalised and of 1 was regarded abnormal, but clinically not relevant. Only 1 patient (6.3%) remained with abnormal clinically relevant ECG finding on day 2 of etrasimod intake. At week 12 and 52 proportion of patients with clinically significant ECG abnormality was slightly higher on etrasimod compared to baseline and to placebo.

Changes in ECG over time

On ECG (placebo-controlled UC pool; first analysis visit on treatment at Week 12 and onwards; mean and median values) no relevant durable changes were observed in heart rate, PR interval, RR interval, QRS and QTcF. QTcF prolongation (mean and median) remained below 5 msec at all times in pivotal UC pool.

Categorical analysis of ECG (placebo-controlled UC pool) showed, that PR interval of >200 msec and especially >230 msec was reported more often in the patients after the first intake of etrasimod 2 mg, than on placebo (7.4% and 2.5% vs. 3.3% and 0.7% on placebo, respectively). No differences were apparent at later stages on treatment. Also, QTcF prolongation by >30 msec was observed more often on etrasimod on day 1, than on placebo (4.5% vs. 2.4%, respectively). Only one case of QTcF prolongation >60 msec was reported for etrasimod at week 12.

AV conduction abnormalities (placebo-controlled UC pool) first-degree AV block was reported in 8% of etrasimod and 3.2% in placebo-treatment arms at Day 1. Second-degree AV block (Mobitz type 1) was observed in 0.4% of the patients on both treatments on day 1. No relevant differences across treatment were observed afterwards over treatment period.

Similar changes were observed in other pools.

Ophthalmoscopy and Optical Coherence Tomography

Measurement of macular central foveal thickness (CFT) was performed using OCT at Screening, Week 12, and Week 52 to screen for treatment-emergent macular oedema. During the review it was noted that the original analysis of the changes in the CFT included mistakes in the data entry. With the response to the Day 180 LoOI, the applicant provided verified updated analysis limited to the APD-334-301 study only (New verified data from 27 Oct 2023). This analysis does not show any differences in the CFT across placebo and etrasimod.

Table 60: Proportions of Participants with Change from Baseline in CFT ≥ 40 µm in Any Eye and Any Visit for Participants with Assessments at Baseline and Week 52 – Safety Set (APD334-301) (New Verified Data 27 Oct 2023)

	Etrasimod 2 mg (N=94) n/N1 (%)	**Placebo (N=26) n/N1 (%)**
Participants with ≥40 µm CFT Change from Baseline	11/94 (11.7)	3/25 (12.0)

N: number of participants with assessments at baseline and Week 52 who have verified CFT data.

N1: number of participants with assessments at baseline and Week 52 who have verified CFT data at both baseline and post-baseline visits. One participant in Placebo has only post-baseline visits verified but baseline not verified, therefore this subject has no verified change from baseline data.

The same subjects with verified data are also analysed using their original data, shown under "Original Data".

Source: Table 0057b.7.3.1; Table 0057b.7.7.2(listing) and Table 0057b.7.2.1

In ophthalmoscopy categorical results of the macula, the proportion of subjects with a shift from normal at Baseline to abnormal at Weeks 12 or 52 was similar in the etrasimod 2 mg and placebo groups in both the Pivotal UC and All UC Pools.

Intraocular pressure

In the Pivotal UC Pool, mean values for IOP at baseline, Week 12 and Week 52, and CFB at Weeks 12 and 52 were not different between treatment arms. Of the 358 participants who received etrasimod 2 mg and had baseline IOP measurements, 11 on etrasimod (3.1%, EAIR = 0.028/PY) and 3 on placebo (1.7%, EAIR=0.050/PY) had elevated IOP (>21 mm Hg).

Participants with a medical history of glaucoma (8 participants) or increased IOP (2 participants) on etrasimod did not experience relevant changes in IOP.

Pulmonary Function Testing

In the Pivotal UC studies, spirometry tests (FEV_1, FVC, and FEV_1/FVC) and DLCO (where available) were performed at the beginning of the study and at post-Baseline timepoints as specified in the study protocol (eg, Week 12, Week 52 [for Study APD334-301 only] or early termination, or when clinically indicated). Subjects were excluded if they had FEV_1 or FVC < 70% of predicted values and FEV_1/FVC ratio < 0.70 at Screening in the Phase 3 pivotal UC studies. Subjects experiencing a decline in FEV_1 and/or FVC below 50% of the predicted values were to be discontinued from study treatment and scheduled for a follow-up visit.

DLCO was not available at all sites across the etrasimod development program and was therefore performed in fewer subjects than spirometry tests.

Limitations

A limitation of these analyses includes the observations that the data includes outlying values reflective of technical issues that may have been related to conduct of spirometry testing by site Investigators rather than pulmonary function during the COVID-19 pandemic. In addition, site standards varied with respect to predictive equations for values and correction of DLCO for haemoglobin, an important factor in subjects with gastrointestinal blood loss.

Overall mean and median values agreed. Mean values are primarily used as a measure of central tendency for PFTs.

Pivotal UC Pool: Beginning at Week 12, reductions in FEV1 and FVC (ie, mean [SD] change from Baseline) were observed for subjects in the etrasimod 2 mg group (FEV1: −0.049 [0.3635] L; FVC: −0.012 [0.4675] L) compared to placebo (FEV1: −0.019 [0.3494] L; FVC: −0.005 [0.4825] L). FEV1 did not decrease further by Week 52 for the etrasimod 2 mg group (FEV1: −0.068 [0.4135] L; FVC: −0.039 [0.6413] L) compared to the placebo group (FEV1: −0.108 [0.4528] L; FVC: 0.008 [0.5858] L). Changes were not considered clinically significant in either treatment group as there was a lack of association of PFT findings to related AEs. The mean changes reported were within the limits of within-person variation in spirometric values between 100 – 200 mL/year.

Changes in FEV1/FVC, or DLCO were similar across treatment groups. The proportions of subjects who had > 20% declines from Baseline in FEV1, FVC, or DLCO were either similar between treatment groups or lower in the etrasimod 2 mg group compared to the placebo group at corresponding timepoints.

All UC Pool: Mean and median changes from Baseline in spirometry assessments at the Week 78 (1.5 years) and Week 104 (2 years) visits were similar to the Week 52 visit for the etrasimod 2 mg group. Decreases > 20% from Baseline in FEV1 and FVC were experienced by single subjects beyond Week 64. Number of patients in this analysis was limited.

With the response to the Day 120 LOQ the applicant performed sensitivity analyses of FEV1 and FVC separately for the two pivotal studies (APD334-301 & APD334-302) and for the pivotal pooled data from these two studies. The results of the analyses indicate that there is no worsening of pulmonary

function during the course of treatment, and the differences between etrasimod and placebo group are not statistically significant nor clinically meaningful. Additionally, subgroup analyses performed in the Pivotal UC pool for change from baseline in PFTs showed that a history of asthma or COPD, or current use of tobacco were not associated with significant differences in change from baseline for FEV1 or FVC in the etrasimod 2 mg arm compared to placebo.

Laboratory values in the follow-up phase

Analysis of select parameters of interest (haematology, chemistry, clotting parameters, heart rate, systolic blood pressure and diastolic blood pressure) in the subset of participants who received etrasimod 2 mg and underwent follow-up investigations revealed decreases in lymphocyte, neutrophil, and platelet counts during the course of treatment with etrasimod 2 mg that showed a recovery effect off-treatment. Review of data for laboratory parameters such as albumin, liver enzymes (ALT, AST, GGT, LDH, alkaline phosphatase), bilirubin, triglycerides, blood urea nitrogen, electrolytes, creatinine, creatine kinase, C reactive protein, and thyroid parameters such as thyrotropin, thyroxine, and triiodothyronine did not reveal any trends to recovery. Review of the data for systolic blood pressure and diastolic blood pressure revealed fluctuations in these parameters over time.

2.6.8.5. Safety in special populations

Adolescents and elderly patients

All age groups in the Pivotal UC Pool and the All Indications Pool who received etrasimod 2 mg had similar mean total study treatment received per subject and mean total exposure to study treatment per subject in weeks.

The ≤ median age and > median age groups had similar total subject-years of exposure. The < 65 years group had considerably higher total subject-years of exposure than the ≥ 65 years group due to the imbalance of subject numbers (pivotal UC pool:< 65 years: N = 498, total subject years = 249.9; ≥ 65 years: N = 29, total subject years = 15.7; All UC pool: < 65 years: N = 1022, total subject years = 804.3; ≥ 65 years: N = 55, total subject years = 47.8).

Table 61: Select Treatment-Emergent Adverse Events by Category, Preferred Term, and Age Group (PC UC Pool)

	Age <65		**Age ≥65 to <75**		**Age ≥75**	
MedRA Terms	**Etrasimod Any Dose N = 597 n (%)**	**Placebo N = 292 n (%)**	**Etrasimod Any Dose N = 29 n (%)**	**Placebo N = 21 n (%)**	**Etrasimod Any Dose N = 3 n (%)**	**Placebo N = 1 n (%)**
Participants with at least one TEAE	359 (60.1)	153 (52.4)	16 (55.2)	9 (42.9)	2 (66.7)	0
Participants with at least one Serious TEAE	28 (4.7)	16 (5.5)	1 (3.4)	1 (4.8)	0	0
- Fatal	0	0	0	0	0	0
- Hospitalisation/prolong existing hospitalisation	26 (4.4)	16 (5.5)	1 (3.4)	1 (4.8)	0	0

MedRA Terms	Age <65		Age ≥65 to <75		Age ≥75	
	Etrasimod Any Dose N = 597 n (%)	Placebo N = 292 n (%)	Etrasimod Any Dose N = 29 n (%)	Placebo N = 21 n (%)	Etrasimod Any Dose N = 3 n (%)	Placebo N = 1 n (%)
- Life-threatening	0	1 (0.3)	0	0	0	0
- Disability/incapacity	1 (0.2)	0	0	0	0	0
- Other (medically significant)	3 (0.5)	4 (1.4)	0	1 (4.8)	0	0
Participants with at least one TEAE leading to discontinuation	31 (5.2)	7 (2.4)	1 (3.4)	1 (4.8)	0	0
Psychiatric disorders	13 (2.2)	4 (1.4)	0	0	0	0
Nervous system disorders	70 (11.7)	21 (7.2)	3 (10.3)	0	1 (33.3)	0
Accidents and injuries (Narrow SMQ)	8 (1.3)	2 (0.7)	1 (3.4)	0	0	0
Accidents and injuries (Broad SMQ)	2 (0.3)	0	0	0	0	0
Cardiac disorders	24 (4.0)	4 (1.4)	1 (3.4)	0	0	0
Vascular disorders	19 (3.2)	7 (2.4)	1 (3.4)	0	0	0
CNS haemorrhages and cerebrovascular conditions (Narrow SMQ)	1 (0.2)	0	0	0	0	0
Infections and infestations	114 (19.1)	48 (16.4)	8 (27.6)	4 (19.0)	0	0
Anticholinergic syndrome (Narrow SMQ)	0	0	0	0	0	0
Anticholinergic syndrome (Broad SMQ)	55 (9.2)	13 (4.5)	3 (10.3)	1 (4.8)	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	24 (4.0)	6 (2.1)	1 (3.4)	0	0	0
Other TEAEs appearing more frequently in older patients						
-COVID infections	29 (4.9)	13 (4.5)	2 (6.9)	1 (4.8)	0	0
-Dizziness events	19 (3.2)	4 (1.4)	1 (3.4)	0	0	0
-Headache events	38 (6.4)	10 (3.4)	3 (10.3)	0	0	0

MedRA Terms	Age <65		Age ≥65 to <75		Age ≥75	
	Etrasimod Any Dose	Placebo	Etrasimod Any Dose	Placebo	Etrasimod Any Dose	Placebo
	N = 597	N = 292	N = 29	N = 21	N = 3	N = 1
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Quality of life decreased*	**N = 468**	**N = 231**	**N = 26**	**N = 15**	**N = 2**	**N = 1**
Week 12	18 (3.8)	12 (5.2)	1 (3.8)	1 (6.7)	0	0

AE = adverse event, CRF = Case Report Form, MCS = Mental Component Summary, MedRA = Medical Dictionary for Regulatory Activities, n = number, N = total number of participants in treatment group, PCS = Physical Component Summary, SMQ = Standardized MedDRA Query, TEAE = treatment-emergent adverse event

Source: Tables 0028a.116.1.1; 0028a.116.2.1; 0028a.116.3.1; 0028a.120.1.1; 0028a.120.3.2.

*Quality of life decreased is summarised for a subset of the PC UC Pool consisting of participants who received etrasimod 2 mg in Studies APD334-301 and APD334-302

The subcategorisation of Serious AE is as recorded on the AE CRF page.

Categories are groups of preferred terms based on SMQ or based on clinical inputs and appearing more frequent in older subjects (COVID infections, Dizziness events, and Headache events).

A response of decreased in quality of life is defined as observed change from baseline PCS score ≤-2 AND observed change from baseline in MCS score ≤-3 at a visit, otherwise it is a non-response. Missing response is considered as non-response.

MedDRA24.1 coding dictionary applied.

The updated All UC Pool (data cut-off 30 August 2022) contains 58 (5.6%) participants ≥65 years of age of whom 3 (0.3%) were ≥75 years of age. This represented an additional 5 elderly participants (≥65 years old) who received etrasimod 2 mg in the updated All UC Pool compared with the original All UC Pool (data cut-off 31 Jan 2022). There were no additional participants ≥75 years old in the updated All UC Pool compared to the original All UC Pool. Mean total exposure to study treatment in the ≥65 years age group increased approximately 30% between the initial and updated All UC Pool.

The updated All Indications Pool (data cut-off 30 August 2022) contains 61 elderly (≥65 years) participants with a mean (SD) exposure to etrasimod 2 mg of 55.33 weeks (41.440) and 64.7 total participant years of exposure in the etrasimod 2 mg group. In the updated All Indications Pool, the increase in the number of participants (all ages) who received etrasimod >2 mg (18 participants in the initial versus 74 participants in the updated pool) was driven by ongoing studies APD334 205 Open Label period in participants with AA and APD334-202 SSA in participants with CD.

Common TEAEs by Age

In the Pivotal UC Pool, the proportion of subjects experiencing common TEAEs was greater in the etrasimod group compared to placebo, in the ≤ pool median (38 years) and > pool median groups (about 30% on etrasimod vs about 20% on placebo). In the subgroup of ≥ 65 years olds (n=31 patients on etrasimod 2 mg; n=17 on placebo) only 7 subjects on etrasimod and only 4 on placebo experienced a TEAE. Overall ratio of subjects with at least one TEAE was lower in older population on etrasimod (32.3% vs 22.6%).

In the Pivotal UC Pool subgroups based on median age showed roughly similar TEAE profile. All individual PTs were experienced by < 10% of subjects in each age group. Headache was consistently the most common PT except in those ≤ the median pool age, and there were no notable differences across groups in the proportions of cardiac, liver-related, or infections PTs.

In the ≥ 65 age group the TEAEs (n (%)) with >1% frequency than on placebo were: Headache 3 (9.7), Asthenia 2 (6.5), Fatigue 2 (6.5), Flatulence 2 (6.5), and Dizziness 1 (3.2).

In contrast to the ≥ 65 years olds, in the < 65 group a smaller proportion of subjects reported Headache (≥ 65: 3 subjects, 9.7%; < 65: 32 subjects, 6.5%) and Asthenia and Fatigue had similar frequency as on placebo. Dizziness was reported with approximately similar incidence (n= 17 (3.4%), as in older group. Additional TEAEs with higher frequency (n (%)) than placebo, which were not reported (at all, or in higher frequency compared to placebo) for older patients were Colitis ulcerative 31 (6.3), Nausea 19 (3.8), ALT increased 11 (2.2), Gamma-glutamyltransferase increased 10 (2.0), Hypertension 10 (2.0), Vomiting 10 (2.0), Blood creatine phosphokinase increased 8 (1.6), Diarrhoea 8 (1.6), Hypercholesterolaemia 8 (1.6).

In the placebo-controlled pool there were only 3 patients with the age of 75 years or older treated with etrasimod (vs. 1 patient on placebo). One patient on etrasimod had 2 TEAEs arthralgia and fatigue. No events were reported on placebo.

In the All UC Pool, all age groups had similar proportions of subjects (around 47-49%) who received etrasimod 2 mg and experienced at least 1 common TEAE. Proportion of patients with TEAE on placebo ranged around 27-31% in all subgroups apart from ≥ 65 group with 17.4%. Notably, only 53 patients on etrasimod and 23 on placebo were included in this pool with 15 and 4 patients experiencing TEAEs respectively.

Colitis ulcerative, COVID-19, Lymphopenia, and Headache were consistently the most common PTs, and there were no notable differences across groups in the proportions of cardiac, liver-related, or infections PTs.

In the ≥ 65 years group compared to the < 65 years group, a larger proportion of subjects reported COVID-19 (≥ 65: 6 subjects, 11.3%; < 65: 67 subjects, 7.5%) and Headache (≥ 65: 6 subjects, 11.3%; < 65: 52 subjects, 5.8%). Similar to the pivotal UC pool, asthenia was more frequently observed in older population.

Only one case of fatigue was reported in ≥75 olds on etrasimod. No other events were observed.

TEAE profile derived from the updated All UC and All indications pools did not differ considerably from the initial analysis.

- Safety of etrasimod in patients <18 years old

As of 15 June 2023, 4 participants (age 12-17 yrs) have been enrolled and dosed with etrasimod. One Subject received etrasimod 2 mg and experienced Grade 1 TEAEs of Headache and Anaemia. No other TEAEs of relevance were reported in this subject.

Subgroup analysis of patients ≥ 18 and <25 years of age

The proportion and EAIRs for participants with ≥1 TEAE in etrasimod group was similar between young and older adults, and in both groups higher compared to placebo. Differences were seen when analysing specific PTs: younger patients more frequently reported AE related to underlying condition - Colitis ulcerative, Anaemia, Pyrexia, Nausea, Vomiting, Abdominal distension, Abdominal tenderness, Constipation, Iron deficiency. EAIRs for SAE were also higher in the younger age group receiving etrasimod compared to older adults, however, still lower than placebo. The most frequently reported

SAEs were also related to underlying UC - Anaemia, Colitis ulcerative, Proctitis, and one Anembryonic gestation, however for SAEs of Colitis ulcerative there was no difference between age groups.

Similar trend was seen regarding TEAEs that led to permanent study treatment discontinuation (higher EAIRs in younger group), and regarding specific PTs leading to discontinuation, younger participants reported more Colitis ulcerative and Bradycardia. No participant in the younger group reported AV block that led to study treatment discontinuation compared with 2 participants in the >25 age group.

No significant differences between age groups were noted regarding laboratory results, except for platelet count. Median change from baseline in platelet count was more pronounced in younger patients compared to older adults at most evaluations up to week 20.

Younger patients also had more pronounced mean changes from baseline to Week 52 in PR interval and in QTcF interval. HR at 3 hours post-dose was numerically more pronounced in younger patients (-8.9 vs -7.1 bpm). There were no clinically relevant changes from baseline to week 52 for BP in either group.

APD334-108 – hepatic impairment study

The study showed that no clear and significant changes in laboratory safety parameters were observed.

HR and blood pressure (systolic and diastolic) decreased during the first hours after etrasimod 2 mg dose intake and gradually and slightly increased during the following 9 days post-treatment.

No relevant and unexpected differences were observed in the ECG parameters of PR interval and QRS duration across various populations. QTcF showed clear increase in patients with severe hepatic impairment with max. mean and median prolongation of 18 and 17 msec at 4 h post-dose, respectively. Maximum changes in other populations for mean and median values were 7 and 6 msecs, respectively. The changes across the subjects with normal, and mildly or moderately impaired liver function were roughly similar.

Table 62: Change in QTcF (Day 1; subjects with moderate and severe hepatic impairment)

Study Population: Safety
Parameter: QTcF Interval (ms)

			Day 1					
Hepatic Impairment	Statistic	Baseline	1 h	2 h	3 h	4 h	5 h	6 h
Moderate Hepatic Impairment	n	8	8	8	8	8	8	8
	mean	441	2	8	3	5	-3	-4
	SD	23.5	10.4	13.5	12.7	13.9	11.8	12.4
	median	439	3	5	2	4	-4	-6
	min	410	-14	-6	-16	-14	-24	-17
	max	475	20	36	18	31	18	22
Severe Hepatic Impairment	n	6	6	6	6	6	6	6
	mean	456	0	11	14	18	11	7
	SD	12.0	5.1	10.6	13.9	10.5	19.0	18.6
	median	456	0	10	8	17	11	4
	min	441	-8	-4	4	6	-19	-10
	max	470	7	26	39	37	31	41

Source: Table 14.3.4.3-2 Summary of Changes from Baseline in 12-Lead Electrocardiogram Data

No AEs were reported and the above changes were not described in the study report.

APD334-112 – renal impairment study

In this study one of the objectives was assessment of cardiac safety. Continuous Holter ECG monitoring was conducted over 2 h prior and 24h after administration of 2 mg etrasimod. Data were analysed by a cardiologist.

One subject in each group had supraventricular tachycardia (nonsustained), and one subject in each group had an episode of nonsustained ventricular tachycardia. No subjects had second degree or higher grade atrioventricular block. The clinical significance of the episodes of nonsustained ventricular tachycardia is uncertain, as nonsustained ventricular tachycardia is observed on 24 hour Holters in 1-2% of normal healthy subjects (Min et al). The applicant has concluded similar cardiac safety for healthy vs. subjects with severe/end stage renal impairment.

Pregnancy, lactation and fertility

Pregnancy

In the etrasimod clinical program as of 30 April 2023, there were 20 reports of pregnancy (maternal exposure/partner pregnancy cases and 1 baby case) reported in the PV database from the etrasimod clinical development program (all indications). Of these 20 cases, there were 7 pregnancies and 7 case reports in partners of male study participants; the remaining 13 pregnancy case reports in female participants reflect 12 pregnancies (2 case reports were for 1 pregnancy: a parent case and a linked baby case; and there was 1 case report of a false pregnancy). Overall, there were 19 pregnancies reported.

Regarding partner pregnancies (7): 2 resulted in healthy babies, there was 1 full term birth with neonatal jaundice that resolved, 1 elective termination, 1 spontaneous abortion, and in 2 cases it was not possible to obtain any further information as consent was not given. Regarding female participant pregnancies (12): one was pre-randomisation (no etrasimod given), there were 2 healthy live births, 1 premature birth with neonatal jaundice and patent foramen ovale, 1 anembryonic gestation, 1 ectopic pregnancy, 1 spontaneous abortion, 4 elective terminations/abortions and 1 false pregnancy.

Lactation

There are no data on the presence of etrasimod in human milk or the effects of etrasimod on the breastfed infant or on milk production. When etrasimod was orally administered to female rats during pregnancy and lactation, etrasimod was detected in the plasma of the offspring, suggesting excretion of etrasimod in milk.

Fertility: Females and Males of Reproductive Potential

The effect of etrasimod on human fertility has not been evaluated. In animal studies, no adverse effects on fertility were observed. In a 28-Day study of the effects on spermatogenesis in male rats, there were no etrasimod-related effects on sperm motility, epididymal or testicular sperm concentration, sperm production rate, or sperm morphology noted at any dose level.

2.6.8.6. Safety related to drug-drug interactions and other interactions

Drug-drug interactions are discussed in the PK part of this document.

Etrasimod is metabolised by several CYPs (CYP2C8, CYP2C9 and CYP3A4). Respectively, it was tested in drug-drug interactions studies with fluconazole (a moderate inhibitor of CYP2C9 and CYP3A4 and strong inhibitor of CYP2C19) and rifampin (a strong CYP3A4 and CYP2C19 inducer and moderate CYP2C8 and CYPC9 inducers). Co-administration of etrasimod to fluconazole and rifampin led to increased and decreased exposures to etrasimod, respectively. Therefore, co-administration of etrasimod with a therapeutic agent or a combination of agents that are moderate to strong inducers of two or more CYPs (CYP2C8, CYP2C9, and CYP3A4) (e.g., rifampicin), of agents that are both moderate CYP2C9 and moderate or strong CYP3A4 inhibitors (e.g., fluconazole) is not recommended.

No dedicated study was conducted on drug-drug interactions with beta-blockers. In subgroup analysis of Phase 3 studies, the co-administration of etrasimod in patients receiving stable beta blockers did not result in additive effects on heart rate reduction.

The initiation of a beta blocker with stable treatment of etrasimod has not been studied.

The effect of co-administration of etrasimod and calcium channel blocker, Class Ia (e.g., quinidine, procainamide) and Class III (e.g., amiodarone, sotalol) anti-arrhythmic medicinal products, QT prolonging, anti-neoplastic, immune-modulating, or non-corticosteroid immunosuppressive therapies have not been studied.

If treatment with etrasimod is considered in patients on Class Ia or Class III anti arrhythmic medicinal products, advice from a cardiologist should be sought (section 4.4, SmPC). Potential interactions with antiarrhythmics (including betablocker and Ca-channel blockers), QT prolonging drugs, immune-modulating, or non corticosteroid immunosuppressive therapies, etc. have already been mentioned in section 4.5 of the SmPC. Which is agreed.

Also, no interactions with vaccinations were investigated. Vaccine studies with fingolimod have demonstrated that the failure to develop humoral as well as cellular response to vaccination is attributed to low lymphocyte counts, which is a pharmacological effect of fingolimod. Vaccinations may be less effective if administered during and for up to 2 weeks after discontinuation of treatment with etrasimod. Population PK/PD analysis of peripheral absolute lymphocyte count response using pooled data from Phase 1, 2, and 3 studies with etrasimod demonstrated that the time for at least 90% of subjects to return to the normal 1.0 and 0.8 × 109/L lymphocyte count thresholds was 8 and 4 days for subjects with UC, and 6 and 3 days for healthy subjects, respectively after stopping treatment with etrasimod 2 mg. The use of live attenuated vaccine may carry the risk of infection and should therefore

be avoided during etrasimod treatment and for 2 weeks after discontinuation of treatment with etrasimod (section 4.4, SmPC).

Exposure of the oral contraceptive containing 30 mcg ethinyl estradiol and 150 mcg levonorgestrel did not decrease after co administration of etrasimod. Slight increase in exposure was observed.

2.6.8.7. Discontinuation due to adverse events

In the placebo-controlled pool, the TEAEs leading to permanent study treatment discontinuation reported in the etrasimod 2 mg group and not experienced by subjects in the placebo group were: Colitis ulcerative, Bradycardia, Sinus bradycardia, Atrioventricular block first degree, Atrioventricular block second degree (Mobitz Type I), Blood alkaline phosphatase increased, COVID-19, Clostridium difficile infection, Diarrhoea, Electrocardiogram T wave abnormal, Liver function test abnormal, Macular oedema, Neurological symptom, Pyrexia, and Weight decreased.

The number of subjects who reported at least 1 Cardiac TEAE leading to permanent study treatment discontinuation in the Placebo-Controlled UC Pool was low (etrasimod 2 mg: 6 subjects, 1.0%, EAIR 0.02; placebo: no subjects), as was the number of subjects who reported at least 1 liver related TEAE leading to permanent study treatment discontinuation (etrasimod 2 mg: 2 subjects, 0.3%, EAIR < 0.01; placebo: 1 subject, 0.3%, EAIR < 0.01). No subjects in the < 2 mg group had Cardiac or Liver-related TEAEs leading to study treatment discontinuation.

Table 63: Treatment-Emergent Adverse Events Leading to Permanent Study Treatment Discontinuation by SOC and PT (Placebo-Controlled UC Pool)

System Organ Class **Preferred Term**	**Etrasimod 2 mg/day** **(N = 577)** **n (%) [EAIR]**	**Etrasimod < 2 mg/day** **(N = 52)** **n (%) [EAIR]**	**Etrasimod Any Dose** **(N = 629)** **n (%) [EAIR]**	**Placebo** **(N = 314)** **n (%) [EAIR]**
Subjects with at Least 1 TEAE Leading to Study Treatment Discontinuation	29 (5.0) [0.10]	3 (5.8) [0.25]	32 (5.1) [0.11]	8 (2.5) [0.07]
Gastrointestinal disorders	13 (2.3) [0.05]	2 (3.8) [0.17]	15 (2.4) [0.05]	4 (1.3) [0.03]
Colitis ulcerative	12 (2.1) [0.04]	2 (3.8) [0.17]	14 (2.2) [0.05]	2 (0.6) [0.02]
Diarrhoea	1 (0.2) [< 0.01]	0	1 (0.2) [< 0.01]	0
Abdominal pain upper	0	0	0	1 (0.3) [< 0.01]
Large intestine perforation	0	0	0	1 (0.3) [< 0.01]
Cardiac disorders	6 (1.0) [0.02]	0	6 (1.0) [0.02]	0
Bradycardia	2 (0.3) [< 0.01]	0	2 (0.3) [< 0.01]	0
Sinus bradycardia	2 (0.3) [< 0.01]	0	2 (0.3) [< 0.01]	0
Atrioventricular block first degree	1 (0.2) [< 0.01]	0	1 (0.2) [< 0.01]	0
Atrioventricular block second degree[a]	1 (0.2) [< 0.01]	0	1 (0.2) [< 0.01]	0
Investigations	5 (0.9) [0.02]	0	5 (0.8) [0.02]	1 (0.3) [< 0.01]

System Organ Class Preferred Term	Etrasimod 2 mg/day (N = 577) n (%) [EAIR]	Etrasimod < 2 mg/day (N = 52) n (%) [EAIR]	Etrasimod Any Dose (N = 629) n (%) [EAIR]	Placebo (N = 314) n (%) [EAIR]
Alanine aminotransferase increased	1 (0.2) [< 0.01]	0	1 (0.2) [< 0.01]	1 (0.3) [< 0.01]
Blood alkaline phosphatase increased	1 (0.2) [< 0.01]	0	1 (0.2) [< 0.01]	0
Electrocardiogram T wave abnormal	1 (0.2) [< 0.01]	0	1 (0.2) [< 0.01]	0
Liver function test abnormal	1 (0.2) [< 0.01]	0	1 (0.2) [< 0.01]	0
Weight decreased	1 (0.2) [< 0.01]	0	1 (0.2) [< 0.01]	0
Infections and infestations	2 (0.3) [< 0.01]	1 (1.9) [0.08]	3 (0.5) [0.01]	1 (0.3) [< 0.01]
COVID-19	1 (0.2) [< 0.01]	0	1 (0.2) [< 0.01]	0
Clostridium difficile infection	1 (0.2) [< 0.01]	0	1 (0.2) [< 0.01]	0
Anal abscess	0	1 (1.9) [0.08]	1 (0.2) [< 0.01]	0
Tuberculosis	0	0	0	1 (0.3) [< 0.01]
Eye disorders	1 (0.2) [< 0.01]	0	1 (0.2) [< 0.01]	0
Macular oedema	1 (0.2) [< 0.01]	0	1 (0.2) [< 0.01]	0
General disorders and administration site conditions	1 (0.2) [< 0.01]	0	1 (0.2) [< 0.01]	1 (0.3) [< 0.01]
Pyrexia	1 (0.2) [< 0.01]	0	1 (0.2) [< 0.01]	0
Malaise	0	0	0	1 (0.3) [< 0.01]
Nervous system disorders	1 (0.2) [< 0.01]	0	1 (0.2) [< 0.01]	0
Neurological symptom	1 (0.2) [< 0.01]	0	1 (0.2) [< 0.01]	0
Blood and lymphatic system disorders	0	0	0	1 (0.3) [< 0.01]
Anaemia	0	0	0	1 (0.3) [< 0.01]
Metabolism and nutrition disorders	0	1 (1.9) [0.08]	1 (0.2) [< 0.01]	0
Dehydration	0	1 (1.9) [0.08]	1 (0.2) [< 0.01]	0
Hypokalaemia	0	1 (1.9) [0.08]	1 (0.2) [< 0.01]	0

[a] Atrioventricular block second-degree Mobitz Type I
Subjects are counted only once per summarisation level per treatment group.
Percentages are based on the number of subjects in the pool.
Source: ISS Table 14.3.1.5.2

In All UC Pool, TEAEs leading to permanent study treatment discontinuation reported in ≥ 2 subjects in the etrasimod 2 mg group included Colitis ulcerative, Colitis, Atrioventricular block second degree (Mobitz Type I), Bradycardia, Headache, Lymphopenia, and Sinus bradycardia.

TEAEs leading to permanent study treatment discontinuation, experienced by ≥ 2 subjects in the etrasimod 2 mg group (and not previously described in placebo controlled or pivotal UC pools) were Colitis, Lymphopenia, and Headache.

TEAEs leading to discontinuation related to TEAEs of interest that occurred in 1 subject in the etrasimod 2 mg group and not previously described in the Placebo Controlled UC Pool included:

- Atrial fibrillation, Herpes simplex meningitis, Latent tuberculosis, Hypoaesthesia, Migraine, Transient ischaemic attack, and Vision blurred.

In all pools, the proportion of subjects with TEAEs leading to treatment interruption was greater in etrasimod 2 mg than in either etrasimod < 2 mg or placebo.

Most TEAEs leading to treatment interruption were reported for a single subject in 1 or more treatment groups by pool. Across all studies, 16 subjects experienced more than 1 TEAE leading to treatment interruption.

2.6.8.8. Post marketing experience

N/A

2.6.9. Discussion on clinical safety

Background and methodology

The safety data package includes 20 completed (15 completed Phase 1, 3 completed Phase 2 (UC and atopic dermatitis [AD]), 2 completed pivotal Phase 3 (UC; Studies APD334 301 and APD334 302)) and 3 ongoing Phase 2 or Phase 3 studies (UC and alopecia areata [AA]).

The ISS has 6 different pools, 5 containing phase 2 and 3 studies and one Phase 1 study. Safety assessment in ISS mainly relies on 3 pools in subjects with UC (target population): the Pivotal UC Pool (2 phase 3 pivotal studies with short and long-term treatment in placebo-controlled setting), Placebo Controlled UC Pool (Phase 2 placebo-controlled study added to the Pivotal UC pool), and All UC Pool (Placebo-controlled UC pool complemented with open-label long-term extension study data).

Data pooling strategy and presented summary are overall acceptable. Although, it must be mentioned, that use of multiple subgroup and subpopulation analyses with variable thresholds applied for presentation of AE incidences, definition of SDEI based on narrowly selected criteria, different thresholds applied for vital signs, ECG parameters and laboratory parameters, analyses done in multiple pools and for various treatment durations do not contribute to clarity of safety profile and complicate the review.

Applied methodologies of AE collection and analyses are in line with current standards.

Safety was assessed based on TEAEs, vital signs, ECG/Holter monitoring, laboratory analyses, Optical Coherence Tomography (OCT) and pulmonary function tests (PFT) data.

TEAEs were presented by incidence rates, exposure-adjusted incidence rates (EAIR) and SDEI by treatment, time-to-onset, causal relationship, severity, etc. EAIRs are considered not reliable and SDEI are mostly too narrowly defined, so that potentially relevant safety information may be missed. Therefore, focus of safety assessment remains on standard evaluation of TEAEs. Relevant deficiency of

the safety database is variable reporting of the apparently same clinical conditions by means of different terms, like "insomnia" and "initial insomnia", and large number of unclear terms, which may be interpreted in different ways, e.g., "sleep disorder", "liver transaminase increased". It may be that variable standards for AE reporting and monitoring of database quality were applied in different clinical studies and/or data "cleaning" is not completed due to inclusion of interim data from ongoing studies. The consequence of the above deficiencies is that considerable number of TEAEs are reported as single events (although these practically describe the same, or similar symptom/condition) and the calculated frequencies are very low. As unclear terms can be interpreted in different ways and do not contribute to the safety assessment the applicant has analysed and discussed all TEAEs of interest in detail and provided this information with the responses to the Day120 LoQ and Day180 LoOI to mitigate the risk of missing safety signals.

With the responses to the Day 120 LoQ the applicant submitted new data from the updated All UC Pool and All Indications Pools (data cutoff of 30 August 2022), which included additional data from ongoing Studies APD334-303 and ES101002 (updated All UC Pool) and data from Studies APD334-303, ES101002, and APD334-205 open-label period (updated All Indications Pool), 1 new study and study population (Study APD334-202 in subjects with CD) not included in the initial ISS was also included in the updated All Indications Pool. Focus on this update is put on the All UC pool only as it contains target population. As it seems no update of the PC UC Pool was done.

Results

In total, the initially submitted safety database contained data from 1107 patients with UC, AD, or AA and 449 subjects from clinical pharmacology studies exposed to any dose of etrasimod. Data cut-off point was 31 January 2022. In the updated All UC Pool a total of 1051 subjects with UC received any dose of etrasimod and had a combined 1106 total subject-years of exposure, including 502 subjects with ≥ 52 weeks of exposure to the etrasimod 2 mg dose, and 117 subjects had ≥104 weeks of exposure by August 30 2022. Total number of the patients with any indication exposed to etrasimod is 1301. The number of patients exposed and the tested treatment duration is sufficient to fulfil the formal requirements of the ICH E1 guideline on Population Exposure and to assess safety of the product in the targeted indication, excluding the subpopulations of adolescents and elderly, which were under-represented (see further).

Exposure to (lower and higher than 2 mg) not recommended doses of etrasimod, especially in the placebo-controlled setting, was overall limited. Consequently, detection of dose-dependency of safety parameters is challenging. Evaluation of safety is focused on 2 mg dose of etrasimod in the target – UC population.

In the pools containing only placebo-controlled data median duration of exposure was very short (13 weeks), which is explained by inclusion of 12-week trials in these pools. In the all UC pool mean treatment duration (SD) with etrasimod 2 mg was 41.98 (27.446) weeks with 37.93 weeks median value and range of 0.1 to 132.9 weeks (max. about 2.5 years), which is explained with higher proportion of long-term treatment settings in this pool.

The majority of the population with UC included in the safety database was white, male, middle aged and Caucasian from Eastern Europe. Reported baseline parameters for activity of the disease suggest an adequate representation of moderate and severe subgroups with slight overrepresentation of moderately diseased patients.

Generally, the studied patient population is representative of the target population, with the exception of adolescents and older/elderly populations, which are under-represented. Additional data from the ongoing studies provided with the responses to the day 120 LoQ are limited (5 new elderly patients

with UC and one adolescent). Exposure and safety data in these subpopulations (especially in adolescents) remains limited.

Populations are fairly well balanced across etrasimod 2 mg and placebo arms in the placebo-controlled pools.

TEAEs

Overall, a higher proportion of patients had TEAEs on etrasimod 2 mg than on placebo in the placebo-controlled pools, which was expected. Data on TEAEs reported on <2 mg dose of etrasimod carry limited informative value.

An absolute majority (about 95%) of TEAEs was of mild or moderate intensity with low rates of TEAEs leading to treatment discontinuation (5% vs 2.5% on placebo). Only one case of death (due to neuroendocrine tumour) was reported in more than 1500 subjects exposed to etrasimod. Drop-outs due to cardiac TEAEs were observed in 0.8% (8 subjects) of the patients (UC and non-UC) treated with etrasimod 2 mg and due to liver-related TEAEs in 0.2% (2 subjects). These data suggest that etrasimod 2 mg has acceptable safety profile.

In the largest placebo-controlled UC population common TEAEs occurring with higher frequency (by ≥ 1% point) on etrasimod 2 mg than on placebo were headache, pyrexia, nausea, dizziness, gamma-glutamyltransferase increased, hypertension, urinary tract infection, Alanine aminotransferase increased, vomiting, blood creatine phosphokinase increased, diarrhoea, flatulence, hypercholesterolaemia, bradycardia.

From the above TEAEs the following have been included as ADRs in the PI: headache, dizziness, GGT and ALT increased, hypercholesterolaemia, bradycardia, urinary tract infection, hypertension (all as common events). This are agreed.

It is agreed that pyrexia is a non-specific AE and that nausea, flatulence, vomiting, diarrhoea may represent symptoms of background disease. Among the cases of blood CPK increased about half was reported after physical exertion and the increased frequency of this event on etrasimod seems to be occasional occurrence. Thus, exclusion of these TEAEs from the ADR list is endorsed.

In the all UC pool, the most frequently reported TEAEs on etrasimod 2 mg, that were not reported as common TEAE or were reported with lower frequency (by ≤ 1% point) in placebo-controlled pool, were Colitis ulcerative, COVID-19, Lymphopenia, Lymphocyte count decreased, Leukopenia, T-lymphocyte count decreased, Neutropenia, Respiratory tract infection, White blood cell count decreased. Increased incidence of Colitis ulcerative and COVID-19 is probably related to longer observation period (that also included pandemic phase) in this pool. Increased reporting of the reduced counts of lymphocytes and neutrophils compared to the placebo-controlled setting may be explained by un-blinding of investigators towards the administered treatment and by their awareness that etrasimod may decrease lymphocyte and neutrophil counts. Decrease in number of lymphocytes is the known and expected PD effect of etrasimod, which manifests relatively quickly after start of treatment. Lymphopenia is therefore included in the list of the ADRs with the frequency "very common". This is agreed. The additional TEAEs reported in the all UC pool are discussed per SOT/groups of conditions of interest below.

One additional ADR that is included in the PI is macular oedema. This event was reported only on etrasimod and is a known class effects of S1P-active drugs. Finally, atrioventricular block has also been included as an ADR of etrasimod with uncommon as frequency based on similar scientific rationale. Both AEs are endorsed as ADRs.

Detailed assessment of TEAEs per SOC/organ system of interest:

Cardio-vascular effects – TEAEs, heart rate, blood pressure, ECG parameters:

Data show that etrasimod has clear effects on HR and AV conduction velocity (decrease), which are most prominent on day 1 and 2 after start of treatment. These effects were not accompanied with symptoms of clinical relevance as a rule and were transient. Relevant changes were reported as TEAEs. It seems that indeed the most pronounced impact on heart rate and AV conduction is manifested within the first 4 hours from start of etrasimod treatment.

Bradycardia and AV conduction delay (AV block) are qualified as ADRs (section 4.8 of SmPC).

The SmPC section 4.8 lists AV block with the frequency "uncommon" and bradycardia with frequency "common". When measured by means of ECG, etrasimod treatment was associated with bradycardia in 33% of subjects (nadir HR below 60 bpm within the first 4 hours), or significant bradycardia in 2.5% (HR nadir below 50 bpm), with PR interval prolongation > 200 msec in 7.4% and higher degree prolongation (>230 msec) in 2.5% of subjects.

In the subgroup of patients without PR prolongation at baseline PR prolongation > 200 msec occurred in 5.1% of patients and PR prolongation > 230 msec occurred in 1.8% of patients on etrasimod. Cardiac TEAEs were reported only in 2.2% of subjects on Day 1 (0 subjects on placebo), indicating, that number of TEAEs is not reflective of actual changes in vital signs. In order to adequately reflect the changes in the heart rate and PR captured on ECG, a short summary of these results was included in the section 5.1 of the SmPC.

Events of hypertension were more frequently reported on etrasimod with rather mild increase in mean/median blood pressure over treatment with etrasimod. Hypertension is also included as ADR in the SmPC. These are agreed.

Besides the above events, a number of other events also occurred on treatment with etrasimod but not/or with lower incidence rate on placebo, which may have causal relationship with etrasimod, considering that S1P are expressed not only in the cardiac cells involved in impulse conduction, but also in cardiomyocytes and endothelial cells. Therefore, events like, atrial fibrillation, extrasystoles, ventricular tachycardia (from phase 1 program), coronary vascular disorder, Peripheral arterial occlusive disease, Cardiac failure chronic, etc., and events not coded under the SOC of cardiovascular disorders, pre-syncope, etc. were discussed, as well as the events suggesting development or worsening of atherosclerosis (myocardial ischemia, ischaemic heart disease, peripheral coldness, atherosclerosis, peripheral arterial occlusive disease, transitory ischaemic attack, etc.). Majority of these events occurred in single patients, were unique terms, resolved and had one or multiple alternative causes. Available data currently do not provide solid evidence to support inclusion of any of these events as an ADR. Additionally, use of etrasimod is contraindicated in the 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 and those 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. Also, intensive monitoring of patients is proposed in the SmPC: patients with

- Significant QT prolongation (QTcF ≥ 450 msec in males, ≥ 470 msec in females).
- Severe hepatic impairment who may be at risk for QT prolongation.
- Arrhythmias requiring treatment with Class Ia or Class III anti-arrhythmic medicinal products.
- Unstable ischaemic heart disease, history of cardiac arrest, cerebrovascular disease (occurring more than 6 months prior to treatment initiation), or uncontrolled hypertension.

- History of symptomatic bradycardia, recurrent cardiogenic syncope, or severe untreated sleep apnoea.

Are to undergo cardiologists consultation prior to start of treatment with etrasimod. Patients with resting bradycardia with heart rate below 50 per min, second-degree [Mobitz type I] AV block, or a history of myocardial infarction or heart failure should be monitored for 4 h after the first dose.

These risk-minimisation measures appear overall acceptable.

Generally, given the fact that patients with relevant cardiac disorders were practically excluded from clinical trials, and since data in more fragile elderly population are very limited, it is recommended that cardiovascular events (arrhythmias, bradycardia, heart conduction blocks/delays, ischemia/coronary vascular disorder, heart failure etc.) and the events possibly related with circulation disorders, e.g., due to bradycardia, arrhythmias, or cardiac conduction disorders (e.g., syncope/pre-syncope, confusion, falls/injuries, etc.) are further observed in post-authorisation phase. Cardiovascular events are primary safety events of interest addressed in the Category 3 surveillance study as described in the RMP.

Eye disorders - Macular oedema – ophthalmoscopy and OCT assessment:
Three cases of macular oedema were reported – two on etrasimod 2 mg and one on placebo. One additional case of Cystoid macular oedema was reported on etrasimod. Macular oedema is included as an ADR in section 4.8 of the SmPC, which is in line with the known class effects of the S1Pactive drugs. Also, a warning, that patients with diabetes mellitus, uveitis, or retinal disease, i.e., those at high risk to develop macular oedema, should undergo ophthalmological evaluation prior to start of etrasimod treatment and as follow-up, during the treatment is included in the SmPC. If symptoms suggesting macular oedema are developed on etrasimod, cessation of treatment is recommended until further ophthalmological examination is conducted. These recommendations are in line with those approved for ozanimod and are agreed.

From the events reported in 2 or more patients in etrasimod group, but not reported on placebo, the following are of interest and were discussed in terms of possible causal relationship to etrasimod: Vision blurred, Papilloedema, Myopia, Visual Impairment, Glaucoma and Pigment dispersion syndrome. Events such as "vision blurred" is a known ADRs for fingolimod. Pooling of the events related to impaired vision in the PC UC Pool showed occurrence of such events (5 cases of "Vision blurred", 2 – "Visual impairment", 1 – "Visual snow" and 1 – Diplopia) with higher frequency on etrasimod compared to placebo (only one event of "Visual acuity reduced") (1.6% vs 0.3%, respectively). Considering the above the applicant complied with the request to include an ADR of Visual impairment with frequency "common" in Section 4.8 of the SmPC with a footnote listing the relevant event terms included (PT Visual impairment and PT Vision blurred). This is agreed.

Three patients developed papilledema on treatment with etrasimod. Additionally, increased volume of optic disc, as a finding associated with an event (SAE) of intracranial pressure, was reported also on etrasimod. These events are of special interest, since papilledema is commonly associated with increased intracranial pressure and may be alarming symptom in a patient. The applicant has presented TEAEs of papilledema in detail. One of the cases was considered to be a result of eye trauma. One of the cases was considered as related to the IMP by the investigator. For the third case, the applicant argues that it is attributed to anaemia or UC. An MRI triggered by the observation of Papilloedema in this patient showed "minimal chronic small vessel ischemic disease" and it was concluded that the findings on the MRI most likely reflect a long-term, pre-existing condition not previously identified since no brain imaging had been performed. Published evidence to support the claim that papilloedema, with or without intracranial hypertension, is known to be associated with inflammatory bowel disease (Walker et al., 1998; Sedwick et al., 1984; Liu et al., 1994; Newton et al., 1994;) and anaemia (Biousse et al., 2003;) was submitted.

One case of intracranial increased pressure was reported as an SAE. Participant had anaemia and was also receiving treatment with mesalazine, both factors that can attribute to intracranial hypertension. The applicant argues that inflammatory bowel disease is also associated with intracranial hypertension (Jewell DP, 1972; Khanna et al., 2018). This is supported by Katsanos et al. (2012) that state that intracranial hypertension in patients with inflammatory bowel disease may occur due to cerebral vein and cerebral sinus thrombosis in patients with defective coagulation mechanisms and hyperviscosity.

Considering the aforementioned, for most of the cases of papilloedema and increased intracranial pressure there are confounding factors that offer alternative explanations for the events. The applicant's argumentation can be accepted.

TEAEs of glaucoma appear to have occurred with similar frequency on etrasimod and placebo and data do not suggest clear causal relationship of these events with the received treatment. The same applies to the events of myopia and Pigment dispersion syndrome, which were uncommon events.

The updated assessment of OCT done for APD334-301 study participants only did not show relevant differences between the changes in the CFT observed on placebo and etrasimod.

Also, the IOP did not show any relevant changes on etrasimod treatment neither in the patients with glaucoma, nor in the overall population.

The applicant recommends as a precaution in 4.4 of the SmPC an ophthalmological evaluation before initiating Velsipity, and at any time if there is any change in vision while taking etrasimod, in alignment with other approved S1P receptor modulators (S1PRMs). The applicant also added an additional warning in Section 4.4 of the SmPC for patients at increased risk of Macular Oedema due to pre-existing conditions (a history of diabetes mellitus, uveitis, or underlying/co-existing retinal disease) for an ophthalmic examination near treatment initiation as well as follow-up evaluations while receiving therapy. This is supported.

Respiratory, Thoracic and Mediastinal Disorders – TEAEs and spirometry tests

In pivotal UC pool proportion of patients with at least one TEAE in this SOC was similar across treatments. TEAE PTs reported by ≥ 2 subjects on etrasimod, but not reported on placebo included Dyspnoea, Rhinorrhoea, Dyspnoea exertional, Nasal congestion, Rhinitis allergic. If grouped together dyspnoea and dyspnea exertional can be considered a common event (6 subjects of 577 in the pivotal UC pool – 1% with the patient with COVID-19 is excluded). Additionally, none of the placebo patients had similar events reported. This raises the question, whether these events could have had causal relationship to etrasimod. The applicant states that no TEAEs of Dyspnoea or Dyspnoea exertional were associated with clinically relevant decreases in PFT results. As per question raised the applicant provided a discussion on these events. Most events had more likely alternative aetiologies, no events led to permanent/ temporary discontinuation and the majority of participants recovered from the event while on treatment The results of available spirometry tests (5 subjects with post-baseline PFTs) ruled out a clinically significant chronic obstructive process.

Pulmonary function parameters showed larger decrease in FEV1 and FVC on etrasimod compared to placebo at week 12 without subsequent worsening by week 52. These changes were claimed to be clinically not significant as there was lack of association of PFT findings to related AEs. No other remarkable differences to placebo were observed in other parameters of respiratory function. Notably, patients with affected pulmonary function were excluded from the studies and the tests were conducted by local investigators, so that the data may be affected by standardisation issues. Further, number of patients undergoing the spirometry dropped over the treatment period. The applicant has conducted a sub-group analysis of respiratory parameters in the patients with mild pulmonary disease (eg, asthma, chronic obstructive pulmonary disease) during Study APD334 301. However, the sample is too small to draw any conclusions. As per request, the Applicant provided sensitivity analyses of PFT

parameters for the two pivotal studies (separately and for the pivotal pooled data) which indicate that there is no worsening of pulmonary function during the course of treatment, and the differences between etrasimod and placebo group are not statistically significant. Additionally, a subgroup analysis of TEAEs and pulmonary function tests in patients with and without pulmonary diseases was provided. Neither a history of asthma or COPD, nor current use of tobacco, was associated with either significant or a consistent pattern of differences in change from baseline for FEV1 or FVC in the etrasimod 2 mg arm compared to placebo. Among the participants in the Pivotal UC Pool, 30 participants in the etrasimod 2 mg arm and 17 participants in the placebo arm had asthma or COPD. There was no increase in TEAEs in the Respiratory, thoracic and mediastinal disorders SOC in patients with history of asthma or COPD compared to the overall study population.

The mean change from baseline in FEV1 and FVC reported are within the limits of within-person variation in spirometric values, they were not accompanied by related AEs, the PFT-related adverse events were reported in higher proportion in placebo group than in etrasimod 2 mg group and no negative trends over duration of treatment were observed.

The SmPC includes a precautionary statement for the prescriber that reductions in absolute forced expiratory volume over 1 second (FEV_1) and forced vital capacity (FVC) were observed in patients treated with S1P receptor modulators, including etrasimod. It advises that etrasimod should be used with caution in patients with severe respiratory disease (e.g., pulmonary fibrosis, asthma, and chronic obstructive pulmonary disease). Which is acceptable.

Infections and infestations

No apparent signals could be detected in the SOC of infections and infestations. It seems, that some events actually describing infections may be spread across various SOCs. Increased risk of infections during treatment with etrasimod is mentioned in the SmPC, which is in line with other medicinal products acting on S1P. It may be that lower respiratory tract infections (PTs bronchitis and pneumonia) have higher frequency on etrasimod. Pooling of similar events of the infections related to lower respiratory tract has revealed that these events occurred in 7 out of 577 patients on etrasimod 2 mg, but no such cases were reported on placebo. The ADR of "lower respiratory tract infection" was included in section 4.8 of the SmPC with the frequency of "common". This is agreed.

Opportunistic infections

When pooled together opportunistic infections occurred more frequently on etrasimod in the placebo-controlled setting than on placebo, i.e., 13 events (2.25%) of opportunistic infections on etrasimod and 5 cases (1.6%) on placebo occurred in the PC UC pool. These events included herpes infections, cytomegalovirus, clostridium difficile, candida infection.

Detailed review of these events did not allow to reveal clear causal relationship with etrasimod, partly due to the presence of multiple con founders. The SmPC includes the warning on increased risk of opportunistic infections. This is acceptable.

Liver injury and laboratory data on hepatic function

Relevant numbers of patients had increased levels of Alanine aminotransferase increased, Gamma-glutamyltransferase increased, Aspartate aminotransferase increased, Blood alkaline phosphatase increased, bilirubin increased, Transaminase increased, Hepatic enzyme increased, etc. on etrasimod 2 mg. On placebo, mostly either no such events were reported, or in lower frequency.

The events of GGT and ALT increased have been added to SmPC as ADRs and risk minimisation measures, like collection of baseline values of liver function parameters, monitoring of symptoms suggestive of liver toxicity and treatment interruption in the event of increased transaminases have also been included in section 4.4. of the SmPC. These measures are considered adequate. However,

some PTs like "transaminases increase", "hepatic enzyme increased", "hepatic enzyme abnormal", "liver function test abnormal", "liver function test increased", "transaminases abnormal" are vague and it needs to be clarified to which liver enzymes do the reported PTs refer to. The applicant provided additional detailed information on the listed events. Majority of these reflected elevated ALT in blood. Re-calculation of frequencies did not, however, change the entered frequency of this ADR in the SmPC. This is agreed.

In the laboratory tests, changes in liver chemistry (ALT, AST, ALP, total bilirubin and gammaGT) values and total cholesterol (non-fasted) parameters on etrasimod 2 mg were observed. However, there were no cases of elevations in liver enzymes/bilirubin that met Hy's Law criteria and clinically relevant elevations of > 3 × ULN and > 5 × ULN were reported for ALT/AST and GammaGT only. While elevated ALT, AST and GGT are reported as ADRs in the PI. This is agreed.

Nervous system disorders

The evaluation of the events grouped under Nervous system disorders remains not comprehensive. Overall, TEAEs related to this SOC were more frequent on etrasimod. The events of dizziness and headache have been acknowledged as ADRs. The question is whether there are other events, which may be suspected as ADRs. This is relevant, since S1P receptors are also known to be located in CNS and as further ADRs aside of "headache" and "dizziness", such as migraine, seizure, Posterior reversible encephalopathy syndrome (PRES) have been known for e.g., fingolimod.

The applicant has provided detailed discussion on various AEs and SAEs falling under the category of nervous system disorders. Concretely, events like migraine, cerebral small vessel ischaemic disease, transitory ischemia, ocular migraine and Vascular encephalopathy were presented in detail. It is agreed with the applicant that the data do not provide sufficient evidence to conclude on a causal association between these events and etrasimod. The events are confounded by use of concomitant treatments, by concomitant diseases, and/or have started without clear temporal relationship to the start of study treatment. In many cases, similar events have been recognised to occur more frequently in the patients with UC.

Three cases of papilloedema on etrasimod (with zero case on placebo) raised suspicion of causal relationship with the drug. More importantly, papilloedema is a well-known sign associated with increased intracranial pressure. However, provided narratives do not reveal apparent link to the treatment with etrasimod.

One SAE of demyelination has been reported on etrasimod. However, it was concluded to be likely related to multiple sclerosis. No test to detect the presence of JC virus has been conducted to exclude the diagnosis of PML and the investigator did not consider this case suitable to forward to adjudication committee for further evaluation. Notably, the first neurological symptom in this patient was reported on study day 386 (episode of altered vision). The patient stayed on etrasimod up-to the day 524 without progression in neurological symptoms and the diagnosis of MS was established more than 1 month after withdrawal from the treatment. It is unlikely that the patient developed PML.

Events which reflect changed cognition (e.g., impaired memory, confusion) and those suggestive of (focal) neurological effects (e.g., impaired speech, impaired mobility/ability to move, seizure) were evaluated in detail, but data did not reveal clear connection with the used etrasimod treatment.

It must be underlined, that various AEs reported on etrasimod resemble the symptoms of PML and PRES. However, these did not lead to the actual diagnosis of PML or PRES, as the events were mostly mild, or moderate in intensity, transitory, resolved without sequel and on continuous treatment with etrasimod, in some cases the events occurred after cessation of etrasimod treatment and almost in all cases multiple confounders (concomitant conditions and/or medications) were present. Moreover,

development of PML has been reported during treatment with other S1P-active medicinal products in the patients with MS.

Warnings regarding PML and posterior reversible encephalopathy syndrome (PRES) are added in section 4.4 of the SmPC. Also, evaluation of PRES and seizures is planned in the post-marketing phase. This is agreed.

Psychiatric disorders

A number of reported TEAEs under the SOC of psychiatric disorders seem to describe similar conditions. The applicant is requested to pool similar terms describing difficulty to sleep (e.g., "insomnia", initial insomnia", "sleep disorder") and anxiety/hyperactivity (e.g., "anxiety", "restlessness", "irritability", attention deficit hyperactivity disorder). Detailed review of these events did not lead to identification of any new ADRs.

Neoplasms Benign, Malignant and Unspecified

The overall incidence rate of malignancies in the All indications pool (2 confirmed malignancies per 1010.7 patient-years of exposure =198 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).

Haemangiomas (2 in liver and 1 of bone) have been reported on etrasimod 2 mg. Non-clinical studies also showed development of haemangiomas. The applicant explains that the effects reported in mice with regard to development of haemangiosarcomas or haemangiomas were consistent with the class effect observed with approved S1P modulators such as fingolimod, siponimod, ozanimod and ponesimod. This finding is believed to be a result of mouse-specific molecular mechanisms (mouse-specific differences in angiogenic and molecular markers), underlying the observed difference in susceptibility of mice to these tumours. Additionally, the applicant has provided a short review of the 3 TEAEs and of the literature, arguing that cases of haemangioma are rather common occurrence in the population. Two of the three events reported were detected accidentally (haemangiomas in the liver) and the third haemangioma (in the bone) was revealed after back pain. All events were considered not related by the investigators. Overall, the argumentation of the applicant seems plausible.

Development of neoplasms is described as class effect in the SmPC. Velsipity is contraindicated in patients with active malignancies. This is accepted.

Haemorrhagic events, embolism, thrombosis

The applicant argues that the events of bleeding on etrasimod were mostly single events of unique terms, which resolved without sequel and were not associated to changes in the laboratory parameters of coagulation as a rule. Rectal haemorrhage, GI haemorrhage, and haematochezia are events to be expected in participants with UC. None of these events was associated with abnormalities in clotting parameters and/or platelets and for a majority of events. No change was made to study treatment in response to the events. Four SAEs were reported in the All UC Pool (Cystitis haemorrhagic, Gastrointestinal haemorrhage, Rectal haemorrhage, and Haematochezia). None of these events had associated abnormalities in clotting parameters or platelets and none of these SAEs were attributed to study treatment by the investigator or the applicant. This argumentation is accepted.

With respect to the events (TEAEs) describing changes in the coagulation parameters, the differences to placebo were small and no major differences between the treatments in the coagulation parameters from the laboratory data were detected.

Association with thromboembolic events has been reported for other S1P-active products (Zeposia and Mayzent lists these events as important potential risks in their RMPs). Review of the thromboembolic events (frequencies and individual case narratives) has not revealed any differences in the frequencies with placebo.

Thus, currently, data do not seem to be suggestive of adverse effects of etrasimod on coagulation parameters/bleeding, thrombosis or embolism.

Endocrine disorders

A higher proportion of TEAEs was observed in Endocrine disorders SOC in etrasimod 2 mg group compared to placebo in Placebo controlled pool and All UC Pool. As a response to a question raised, the applicant provided a discussion focusing on the events of hyperthyroidism and hypothyroidism as they were reported with higher frequency than other events in the same SOC, and thyroid was one of the target organs identified in rat toxicity studies. Nonclinical data observed with etrasimod in rat are considered rodent-specific with little human relevance. For some of the events in patients receiving etrasimod 2 mg alternative explanations were suggested (pre-existing thyroid disease, corticosteroid use), while some of the events started on day 1 of the study, before the initiation of etrasimod treatment. Most of the events were mild, warranting no study treatment discontinuation and no interventional treatment. A causal association with etrasimod treatment was not established.

Subgroup analyses of TEAEs*:*

Subgroup analysis of TEAEs based on sex, race, ethnicity and region did not show any apparent major differences in TEAE profile, but the results carry low level of certainty due to the limited representation of non-white, non-Caucasian population, in the subgroups of race and ethnicity.

Conducted subgroup analysis of TEAEs with onset time during the first 4 weeks, >4 weeks to 24 weeks, longer than 24 weeks, longer than 1 year on treatment with etrasimod did not show increased frequency of TEAEs on long-term use. Highest frequencies were reported within the first 4 weeks of etrasimod. Weakness of this analysis is that patient numbers decreased with longer treatment duration and the data may be biased through drop out of those poorly tolerating etrasimod.

SAEs, Deaths and other relevant events

Overall proportion of patients with at least one SAE was relatively low and did not differ relevantly between etrasimod and placebo. Majority of the SAEs occurred in single patients and can be assumed to be not related to etrasimod. The following SAEs reported on etrasimod, but not on placebo are of special interest and should be discussed: Migraine, Intracranial pressure increased, Coronary artery disease and Hepatic enzyme increased. From OL setting Iron deficiency anaemia, Gastroenteritis, and Transient ischaemic attack were experienced by ≥ 2 subjects and should also be discussed. Additionally, the following SAEs are of interest in terms of potential causal relationship to etrasimod: chronic sinusitis, herpes simplex meningitis, fine motor skill dysfunction, atrial fibrillation, uncoded events (disturbance of consciousness, worsening of depression), fatigue, accident, pancreatitis, pneumonia, pyelonephritis acute.

Number of TEAEs leading to treatment discontinuation was higher on etrasimod compared to placebo but can be considered overall relatively low (6.6% in all UC population), suggesting overall acceptable safety profile of etrasimod. TEAEs leading to treatment discontinuation were mostly reported in single patients. TEAEs which showed trend were the TEAEs, which are considered ADRs: AV conduction blocks, bradycardia, lymphopenia and headache.

Three SAEs were reported under the SOC of Pregnancy, Puerperium, and Perinatal Conditions SOC: Abortion spontaneous, Anembryonic gestation and Ectopic pregnancy. (see below)

Clinical pharmacology pool

Safety profile of etrasimod 2 mg in clinical pharmacology pool roughly resembles its profile in Phase 2 and 3 trials, particularly for more frequent TEAEs. TEAEs like sinus arrest and ventricular tachycardia were not reported in patient population. However, these events were transitory and ventricular tachycardia (as a single event) was not considered drug-related. Overall, this pool does not raise additional safety concerns.

Laboratory parameters

As expected lymphocytes and TBNK Panel Results reflect the expected effects on T-lymphocytes. Lymphopenia is a known effect of etrasimod and included as an ADR in the product information of Velsipity, which is endorsed.

Decrease in the absolute numbers (mean values) of neutrophils were reported starting from week 2 (the first assessment time point) of etrasimod treatment (2 mg) with no/smaller changes observed on placebo. The median number of neutrophils decreased by more than 20% compared to baseline on etrasimod treatment and 27 patients (>2%) had TEAE describing reduction in neutrophils reported with zero cases on placebo. Additional analysis of neutrophil counts sorted by various Grades confirmed the presence of small but detectable difference to placebo. Neutrophils express S1P receptors 1, 4, and 5. Since etrasimod acts as a partial agonist at S1P4 the causal relationship between the reduced number of neutrophils and treatment with etrasimod cannot be excluded. Therefore, decreased counts of neutrophils was added in section 4.8 of the SmPC as an ADR.

Changes in the mean/median numbers of platelets on treatment with etrasimod were less pronounced (mostly below 10%). Only two subjects had the event of thrombocytopenia experienced, which resolved without treatment interruption. There seems to be insufficient evidence currently for justification of inclusion of decreased thrombocyte counts as ADR.

No relevant differences to placebo for coagulation parameters, urinalysis were observed. However it has been noted that a number of TEAEs related to changes in the coagulation parameter have been reported. These, however, did not deem to show apparent pattern that would suggest obvious causal relationship to treatment with etrasimod.

In the UC Pools, median total cholesterol (non-fasted) in in the etrasimod 2 mg group increased from Baseline beginning at Week 2 and with increases noted through Week 52 with the magnitude of the median change from Baseline was greater at Week 52 than Week 2.

The applicant claims that all changes in the laboratory values return to baseline levels after completion or discontinuation of treatment. Indeed, almost all parameters appeared to return, or at least changed towards baseline levels, at week 2 and 4 after the last dose of etrasimod 2 mg. However, number of patients with follow-up measurements is very low and comparisons to the values on treatment are difficult. The applicant has submitted additional analysis and discussed the changes in various parameters after cessation of treatment with etrasimod. The conclusion is that not all parameters (e.g., liver parameters) recover over the time period tested (2-4 weeks after the last dose). Withdrawal effects after cessation of treatment with etrasimod have not been evaluated.

Special populations

PTs reported more frequently in the ≥ 65 age group were headache and asthenia in the Pivotal UC Pool with addition of COVID-19 in the All Indications Pool. The most frequent SAE PT in this group was in the Infections and infestations Category (PT COVID-19, 3 subjects, 5.0%). The ≥ 65 age group had greater proportions of subjects who experienced SDEI in the Infections and Cardiovascular events Category compared to subjects in the < 65 group in the Pivotal UC Pool. However, drawing robust conclusions on this limited dataset is not possible. Also, long-term treatment data in this subpopulation is very limited.

No dose adjustment in elderly is proposed. While PK (and even PD effects) of etrasimod may be similar across age groups, the clinical meaningfulness, and the consequences for patients' health of the PD effects may differ. As an example, changes in heart rate and blood pressure caused by etrasimod may be well tolerated by a young patient, but may lead to AEs in the multi-morbid elderly population with atherosclerosis, ischaemic heart disease, hypertonic heart disease, etc. Use in elderly patients is considered missing information in the RMP. Due to limited experience with treatment of elderly patients in the etrasimod clinical studies potential impact of adverse events on elderly patients are not fully characterised.

Adolescents were hardly represented in the clinical program. Only 4 subjects were treated with etrasimod within the age range of 16 to <18 years old by the data cutoff 30 August 2022. Reanalysis of data from development program in order to compare young (under 25 years of age) and older adult patients is burdened with low numbers in the younger age group but consistently point to a possibility that younger patients might have somewhat different safety profile compared to older adults. It is acknowledged that this is not a firm conclusion, but rather remains an uncertainty. Data in younger children will be generated according to the approved PIP and are expected to fully address the remaining uncertainty.

Paediatric data for other compounds from the same class are available only for another indication (i.e. multiple sclerosis) but are, however, reassuring.

A concern for patients with a weight below 40 kg, which is expected to occur more frequently in 16-17 year-old compared to older patients, is the model-predicted 1.5-fold increase in exposure of etrasimod. Safety data are essentially absent in this weight group and therefore a statement to treat these patients with caution was included in the product information. This is agreed.

No AEs were reported in the hepatic impairment study and no significant changes in laboratory values have been observed. Vital signs changed as expected. The subjects with severe hepatic impairment tended to have more pronounced decrease in HR and blood pressure few hours post 2 mg etrasimod dose compared to other groups. Significant transient prolongation of QTcF was observed only in subjects with severe hepatic impairment at 4 hours post-dose. The applicant argues that the patients with severe hepatic impairment may be more susceptible to development of prolonged QT and has included severe hepatic impairment as a contra-indication in the PI. This is agreed. Since it is unclear whether the M3 and M6 metabolites might have contributed to QT prolongation and considering that M3 and M6 have not been accepted as minor metabolites, *in vitro* evaluation of their potential to prolong QT should be evaluated. The applicant proposes to conduct a post-approval non-clinical evaluation of M3 and M6 on hERG. This is agreed. The applicant states that it is not expected that similarly high levels of the M3 and M6 metabolites may be reached in other clinical situations/populations (e.g., via DDI).

In renal impairment study no specific AE pattern could be identified. Vital signs changed to roughly similar extent in subjects with and without renal impairment. Abnormal ECG was reported in larger portion of subjects with renal impairment already at baseline (around 63% vs. 38% in subjects with normal renal function), therefore, higher frequency of arrhythmia (i.e., premature ventricular complexes) reported in this group may also be a chance finding.

Drug-drug interactions

Drug-drug interactions related to CYP are discussed in more detail in the PK part of this document.

Subgroup analysis of ECG and HR in patients with betablockers is reassuring at least to some extent and within the context of strict contraindications and adequate safety warnings included in the SmPC are acceptable.

No dedicated DDI data vs Class Ia and Class III anti-arrhythmic substances and QT prolonging substances have been conducted, but potential interactions are mentioned in the PI. This is acceptable.

Since exposure of oral contraceptives is not reduced after co-administration of etrasimod, their joint use is acceptable. However, there is a concern, that increased exposure of contraceptives may increase the risk of thrombosis. Provided safety data, however, do not show an increased frequency of thrombosis or embolism. Therefore, no further action is deemed currently warranted.

Because of the risk of additive immune effects, appropriate caution should be applied when Anti-Neoplastic, Immune-Modulating, or Immunosuppressive therapies are co-administered with etrasimod. No data are available on the efficacy and safety of vaccines in patients taking etrasimod. The related precautionary statement in 4.4 of the SmPC is considered acceptable. Vaccines may be less effective if administered during etrasimod treatment. The failure to develop humoral as well as cellular response to vaccination has been attributed to low lymphocyte counts, a pharmacological effect of fingolimod treatment. Population PK/PD analysis of peripheral absolute lymphocyte count response using pooled data from Phase 1, 2, and 3 studies demonstrated that the time for at least 90% of subjects to return to the normal 1.0 and 0.8 × 109/L lymphocyte count thresholds was 8 and 4 days for subjects with UC, and 6 and 3 days for healthy subjects, respectively after stopping treatment with etrasimod 2 mg. Due to the theoretical risk of infection with the use of live attenuated vaccines while taking an S1P receptor modulator, in the Pivotal UC studies, use of a live vaccine was prohibited ≤ 4 weeks prior to randomisation, during treatment, and within 8 weeks after the last dose of study treatment. In section 4.5. of the SmPC it is stated that the use of live attenuated vaccine may carry the risk of infection and should therefore be avoided during etrasimod treatment and for 2 weeks after discontinuation of treatment with etrasimod. The SmPC advice is consistent with similar warnings provided in the labelling for other S1P receptor modulators, based upon the respective, effective half-lives of these drugs, timing of lymphocyte count decrease upon treatment initiation, and time required to recovery of peripheral lymphocyte counts to normal range upon cessation of therapy.

Pregnancy, Puerperium, and Perinatal Conditions SOC

Overall, with the submission of the response to the Day 180 LoOI (data cut-off 30 April 2023), there were 19 cases (maternal exposure/partner pregnancy cases and 1 baby case) of pregnancy in etrasimod clinical development program (all indications), 7 pregnancies in partners of male study participants and 12 in female study participants (of these 12, 1 took place pre-randomisation, i.e., without exposure to etrasimod and 1 was a false pregnancy). In partner pregnancies, at least 1 pregnancy had non-physiological end (spontaneous abortion). In female participants (where data are available) at least 3 were non-physiological (1 anembryonic gestation, 1 ectopic pregnancy, 1 spontaneous abortion) and 4 were interrupted by elective terminations/abortions (reason unknown). Considerable number of pregnancies can be regarded to as pathological. Also, out of 6 live births, 2 were premature. Velsipity is contraindicated during pregnancy.

Based on animal studies, etrasimod may cause foetal harm. Therefore, etrasimod is contraindicated during pregnancy and in women of childbearing potential not using effective contraception (section 4.3 of the SmPC). Section 4.4 of the SmPC also specifies, that "Before initiation of treatment, women of childbearing potential must be informed to this risk to the foetus, must have a negative pregnancy test, and must use effective contraception during treatment and for at least 14 days after treatment discontinuation." In the package leaflet the following warning is included:

"Pregnancy and contraception.

Do not use Velsipity during pregnancy, if you are trying to become pregnant or if you are a woman who could become pregnant and you are not using effective contraception. If Velsipity is used during pregnancy, there is a risk of harm to the unborn baby. If you are a woman who could become pregnant, your doctor will inform you about this risk before you start treatment with Velsipity and will

ask you to do a pregnancy test in order to ensure that you are not pregnant. You must use effective contraception while taking Velsipity and for at least 14 days after you stop taking it. Ask your doctor about reliable methods of contraception.

Your doctor will give you a patient card which explains why you should not become pregnant while taking Velsipity.

If you do become pregnant while taking Velsipity, tell your doctor straight away. Your doctor will likely stop treatment (see "If you stop taking Velsipity" in section 3) and pre natal checks will be performed to monitor the health of the unborn baby."

The proposed warnings are, overall acceptable.

There are no clinical data on breastfeeding and impact on fertility. Breastfeeding is not recommended during treatment with etrasimod as per product information (SmPC and PL) which is acceptable.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.10. Conclusions on the clinical safety

A sufficiently large safety database is available to describe the safety profile of etrasimod in adult patients with UC.

Overall, the safety evaluation revealed a low proportion of subjects with TEAEs and SAEs, small differences to placebo and a broad variety of the unique terms, which were reported in single patients mostly. Combined with predominantly mild severity of the events and low rates of study withdrawals due to TEAEs, an acceptable safety profile is assumed. Key adverse events, which became apparent and are clearly related to etrasimod are bradycardia and AV conduction delays, which were more pronounced during the first 2 days from start of the treatment and mostly resolved without countermeasures. Increased levels of ALT, AST and GGT have also been reported. Overall, most frequent adverse events, changes in laboratory parameters, ECG and vital signs reflect known PD effects of etrasimod and are consistent with the known safety profile of other S1P-active substances.

Safety data in adolescents (16 to <18 years of age) and in elderly is very limited. These limitations have, however, been mentioned in the SmPC. Post-approval collection of safety data on the important potential risks such as e.g., PRES and seizures and of the missing information in the elderly, is committed by the applicant by means of an Active Surveillance, Post-Authorisation Safety Study. Furthermore, the applicant will broaden the safety database when submitting the final results of the Open-Label Extension Study APD334-303. Both studies are category 3 studies in the RMP.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 64: 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

2.7.2. Pharmacovigilance plan

Table 65: 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-Authorisation 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 characterisation purposes, incidence rates will also be estimated among patients who initiate other advanced UC therapies.	The following are the primary safety events of interest addressed: • 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	Protocol draft submission Interim report submission Final study report submission	Within 6 months from approval of etrasimod by the EC Within first quarter of year 5 of the study Within 6 months from the end of data collection

Table 65: On-going and Planned Additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestone	Due dates
		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

2.7.3.
Risk minimisation measures

Table 66: 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)
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

Table 66: Summary of Risk Minimisation Measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
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)
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)

Table 66: Summary of Risk Minimisation Measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
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)

2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.6 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 12.10.2023. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Velsipity (etrasimod) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The applicant claimed the following indication:

"Velsipity is indicated for the treatment of patients 16 years of age and older with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or an advanced treatment."

The CHMP did not accept the term advanced therapy in the indication as this is clearly defined in the EU and refers to a medicine for human use that is based on genes, cells or tissue engineering. Development and approvals of advanced therapies are a subject to specific guidelines, requirements, directives and legally binding regulations (e.g. Regulation (EC) No 1394/2007) which did not apply for the development or approvals of medicinal products such are JAKi or biologics.

The applicant amended their claim to "advanced immunomodulators" (referring to biologics and small molecules). However also the number of patients included in Phase 3 studies which have been treated with small molecule immunomodulators with a specific mode of action (i.e. JAKis) was limited to 53 patients overall, and to 24 patients not having also received a biologic previously.

The efficacy in this subpopulation of 24 patients with JAKi only (a total 50 with exposure to JAKis and biologics) pre-treatment showed similar response to the overall population but only for the short-term treatment since there were almost no patients in the chosen response-efficacy categories with a previous JAKi treatment only in the long-term part of study 301 (only for the endpoint symptomatic remission, with an evaluation based on 10 patients). A conclusion on "similar efficacy" in those with JAKi pre-treatment was not considered acceptable by the CHMP based on these results.

Accordingly, the applicant finally amended the indication further exchanging the term "advanced treatment" with "biological agent" (see approved indication further below).

Ulcerative colitis (UC) is a chronic gastrointestinal inflammatory disorder that involves the surface mucosa, the crypt epithelium, and the submucosa of the colon. Patients with UC suffer from diarrhoea, rectal bleeding, weight loss, abdominal pain, fever, and an increased risk of colorectal cancer, which can have a profound impact on patients' quality of life.

The pathology of UC is characterised by a life-long chronic course of remissions and exacerbations.

3.1.2. Available therapies and unmet medical need

Currently there is a wide variety of substances available to induce and maintain remission of ulcerative colitis, including the old substances based on 5-ASA (that are in principle restricted to the treatment of mild to moderate disease), corticosteroids, and "conventional" immunosuppressants. For patients failing on these therapies, biologics (anti-TNFs (infliximab, adalimumab), anti-integrin antibodies (vedolizumab), anti-IL23 antibodies (ustekinumab, mirikizumab), as well as JAK inhibitors (tofacitinib, upadacitinib, filgotinib), and also the first representative of S1P modulators, ozanimod, are available.

Patients treated on any of the available therapies mentioned may be faced with loss of response in the long-run, and any therapy which broadens the armamentarium can be considered to address a "partial unmet medical need".

3.1.3. Main clinical studies

The two phase 3 trials conducted were randomised, double-blind, and placebo controlled studies, with a 2:1 randomisation to active or placebo. One trial (study -302) had a "standard" induction trial duration of 12 weeks, and evaluated efficacy at this time point only. Patients finalising this study were allowed to be included into an open-label, long-term safety study, which has also already presented with final study report for this submission. The other phase 3 trial (study -301) had a so-called "treat-through" design, which kept all patients in their randomised arms for the whole treatment period of 12 months, to account for the need to document long-term efficacy in this disease.

Both trials were appropriately sized to confirm the assumed results based on the previously conducted phase 2 study, and the planning of study -301 took into account the fact that both, short-term (12 weeks) as well as long-term treatment was to be documented and efficacy to be shown. Study 302 included 354 patients (238 for etrasimod 2 mg, and 116 for placebo), and study -301 included 433 patients (289 etrasimod, and 144 placebo). The choice of the 2 mg dose as the only dose taken forward into phase 3 is considered appropriate.

In study 302 the applicant evaluated efficacy with the primary endpoint "proportion of subjects achieving clinical remission at Week 12 with clinical remission defined as a composite of the MMS components with SF=0, or 1 with a ≥1-point decrease from baseline, RB=0, and ES ≤1 excluding friability". The applicant assigned three different "key secondary endpoints" which included "proportion of subjects achieving endoscopic improvement at Week 12 with endoscopic improvement defined as an

ES of 1 or 0 (excluding friability)", proportion of subjects achieving symptomatic remission at Week 12 defined as an SF of 0 or 1 (in case there is an at least 1-point improvement) and RB=0, and "proportion of subjects with mucosal healing at Week 12 defined as ES of ≤ 1 (excluding friability) with histologic remission measured by a Geboes Index score < 2.0". These "key secondary endpoints" were part of a hierarchical testing structure, and hence part of the confirmatory approach of the study. "Other secondary" and "explorative secondary endpoints included a multitude of additional evaluations, including different success criteria, or evaluating the course of the endpoints above over time. Three methods for histological evaluation were also part of these endpoints, as well as the total MS, the investigation of relevant health related QoL scales (IBDQ as a disease specific scale), the evaluation of urgency and abdominal pain as additional symptoms, and the evaluation of biomarkers such a faecal calprotectin and CRP.

Study 301 included the same endpoints (including the hierarchy) for the week 12 evaluation but also defined the same as well as additional secondary endpoints for the week 52 evaluation. The primary endpoint was therefore a co-primary evaluation of the "clinical remission" endpoint defined as above, and the "key secondary endpoints" included all four above endpoints also for the 2 different time-points, as well as additionally, the endpoints "proportion of subjects, in clinical remission at Week 52 and who had not been receiving corticosteroids for ≥ 12 weeks" as well as "proportion of subjects achieving clinical remission at both Weeks 12 and 52".

3.2. Favourable effects

In study 302, the treatment with etrasimod led to "clinical remission" (as defined by the applicant) in almost 25% of the patients (placebo 15.2%), and endoscopic improvement in 30.6% (placebo 18.8%), a symptomatic remission in 46.8% (29.5%), and a mucosal healing of 16.2% (placebo 8.9%). All these results were statistically significant, and the vast majority of "other" and "exploratory" secondary endpoints were in full accordance with these results. Similarly, the additional and sensitivity analyses conducted by the applicant yielded similar results even after re-calculation with different imputation methods for missing values.

In study 301, 27.0% achieved clinical remission at week 12 (7.4% with placebo, 35.0% achieved endoscopic improvement (placebo 14.1%), 46.0% achieved symptomatic remission (placebo 21.5%), and 21.2% achieved mucosal healing (placebo 4.4%). All these results were highly statistically significant, similar to the vast majority of the "other" and "exploratory" endpoints tested.

At week 52, study 301, 32.1% of the patients were in clinical remission (placebo 7.4%), 37.2% had endoscopic improvement (placebo 10.4%), 43.4% had symptomatic remission (placebo 21.5%), and 26.6% had mucosal healing (placebo 8.1%). The proportion of patients in corticosteroid-free remission was 32.1% (placebo 6.7%), and 17.9% of the patients had clinical remission at both the 12-week as well as the 52-week time-points. The post-hoc evaluation of the corticosteroid-free endoscopic improvement at week 52 showed a success rate of 26.4% (as compared to 5.0% on placebo), and a corticosteroid free symptomatic remission rate of 43.4% (placebo 18.5%).

Similar to the early time-point, the vast majority of "other" and "exploratory" endpoints also showed high statistical significance.

The symptomatic improvements occurred as early as 2 weeks, and statistical superiority of placebo could be demonstrated from this early time-point almost fully consistently across the whole duration of the study.

For both studies (and for both evaluation time-points), relevant subgroup evaluations were presented according to sex, age, race, region, and baseline intake of corticosteroids, previous treatment failure,

and disease severity. The subgroup results showed increased variability with subgroups partially not achieving statistical significance. Some of the subgroups showed variation across the two studies (with the 12 week evaluation), which thus levelled out when the results were pooled. As expected, or as seen in previous developments, there was a somewhat reduced effect in patients that had long-standing and widespread (pancolitis) disease, and there was reduced efficacy for those patients that had previously received unsuccessfully an anti-TNF agent, or more than one biologic/JAK-inhibitor treatment. As mentioned, the results were consistent for the subgroup of patients with proctitis only, and for those with MMS of 4.

It is noted that in this programme, consistently, the improvement of symptoms was larger (higher rates of improvement or remission, respectively) than those for the endoscopic mucosa evaluation.

3.3. Uncertainties and limitations about favourable effects

The primary endpoints proposed were not chosen in accordance with the CHMP UC guideline, which would require the co-primary evaluation of "mucosal healing" and "symptomatic remission" in short-term trials, and the co-primary evaluation of these two with the condition of patients being free of corticosteroid treatment. For the study 302, and the short-term evaluation of study 301, the key secondary endpoints included the endpoints required in the CHMP UC guideline (mucosal healing at Week 12 defined as ES of ≤ 1 (excluding friability) with histologic remission measured by a Geboes Index score < 2.0) and can be accepted. The week 52 evaluation of study 301 did only define the "composite remission" endpoint of the three components of the mMS as corticosteroid free. A couple of other endpoints reported also corticosteroid-free rates of improvement out of the "other" and "exploratory" endpoints, but the "corticosteroid-free symptomatic remission" endpoint was only evaluated post-hoc, although the requirements of the CHMP UC guideline have extensively been discussed in a Scientific Advice procedure. Nevertheless, since the overwhelming majority of endpoints showed consistent statistically significant superiority over placebo, the post-hoc evaluation of this endpoint is not considered to be a major deficiency.

The applicant has applied a "composite strategy" with regard to estimands (according to the ICH E9 addendum), both for the early time-point of week 12, and also for the late time-point week 52. However, the CHMP UC guideline rather recommends to use a "treatment policy" strategy for the early evaluation time-point, and a composite strategy for the late (long-term) efficacy evaluation time-point. The concern derived for the current study programme relates mainly to the fact that the early treatment discontinuation was either not handled according to the recommendations of the UC guideline or occurred so frequently and in differential manner between the treatment groups. In the short-term trial 302, and for the early evaluation of study 301, the number of these treatment discontinuations was small or at least relatively small and would be regarded not to cause concern. However, such treatment discontinuations (either due to disease worsening or due to lack of efficacy) was very high, ending in rates of completion of the treatment of only 31.9% in the placebo, and 57.4% in the active treatment group. While the differential rates of discontinuation due to the mentioned two reasons might also be taken as an indicator of efficacy (and certainly is one), uncertainties especially arise when evaluating "nominal" endpoints, when the majority of data are in fact missing (and for which a separate estimand was not defined). This applies to the (numerical) evaluations of the total MS, the partial Mayo Scores, the evaluations of histology, the evaluation of the scales for health-related Quality of Life, as well as for the biomarkers CRP and faecal calprotectin. For part of these, the applicant has reported an analysis based on observed data in the first place (e.g. based on 38 and 152 patients of the originally 135 and 274 patients), which is not considered appropriate and did not result in a demonstration of statistical significance for some of these parameters. However, the re-analyses of these data with different imputation methods overall showed robustness of the results which is

considered reassuring. Still, an evaluation of the full time-course of efficacy/response is somewhat hampered by the high occurrence of IEs.

As mentioned, the applicant has conducted so-called "additional" sensitivity analyses (altogether four) mostly to explore different types of missing data approaches. These were partly not properly reported in the study reports, and the conducted tipping point analysis was not fully understood. The re-analyses presented at request, were, however, considered fully acceptable and supported the primary analysis.

Also, there was a protocol amendment during the course of the study, which changed the criteria for the discontinuation (from a threshold-based RB and SF in any of 2 time-points to more precisely described RB and SF criteria "for 2 time-points at least 7 and no more than 14 days apart"). This amendment has been shown to have served its purpose (reduce the number of discontinuations) but seem not to have introduced a differential handling of discontinuations with regard to the difference between active and placebo treatment.

In conclusion, while estimand definitions and missing data imputation strategies could be finally accepted, the remaining uncertainties are considered minor after presentation of adequate re-analysed data.

The applicant has evaluated an endpoint "time-to-disease worsening" during the long-term treatment phase of study 301 which was intended to take account of the possibility of patients to be discontinued from the due to exit criteria. The endpoint, however, failed to demonstrate statistical significance, which was potentially based on a wrong analyses which included only the responders at week 12.

A reduction of the overall effect is also detected in those patients "heavily pre-treated" with more than one biologic/JAK inhibitor. This is not unexpected and has been demonstrated to be within the results of other trials in the field.

Endpoints analysed at week 12 in study 301 study were not fully replicated in study 302 study with some reduction of the treatment effect over placebo. With additional analyses presented at request, the applicant has made likely that the observed differences are mainly attributable to the baseline characteristics of the population included in study 302 and the effect size is within the ranges observed historically. The remaining concern has therefore been resolved.

Similarly, the potential for functional unblinding (due to HR decrease at Day 1 when patients were monitored) and hence the introduction of potential bias has been made unlikely by the applicant.

3.4. Unfavourable effects

The safety profile of the recommended dose of 2 mg etrasimod is based on 1556 subjects including 942 patients with UC, which contribute 757.9 total subject years of exposure. Data on long-term treatment, for at least 24 weeks (6 months), 52 weeks (1 year) and 104 weeks (2 years) in the target population are available for 666, 281 and 27 patients with UC, respectively.

Overall, etrasimod was well tolerated, with a low rate of discontinuations due to AEs and a similar incidence of SAEs to placebo. The most prominent events known for S1P-acting drugs were decrease in heart rate and AV conduction delay (AV block first and second degree), which manifested typically on day 1 of etrasimod treatment (mostly within the first 4 hours from the start), were transient and resolved mostly without countermeasures by day 2. Notably, when evaluated by means of ECG analysis and vital signs, etrasimod treatment was associated with bradycardia (nadir HR below 60 bpm within the first 4 hours) in 33% of subjects, or significant bradycardia in 2.5% (HR nadir below 50 bpm), with PR interval prolongation > 200 msec in 7.4% and higher degree prolongation (>230 msec)

in 2.5% of subjects. In the subgroup of patients without PR prolongation at baseline PR prolongation > 200 msec occurred in 5.1% of patients and PR prolongation > 230 msec occurred in 1.8% of patients on etrasimod. Contrary to this, cardiac TEAEs were reported only in 2.2% of subjects on Day 1 (0 subjects on placebo), indicating, that only a fraction of HR and AV conduction changes was considered sufficiently significant to report as a TEAE. On repeated treatment with etrasimod similar events were either not reported or decreased, reflecting development of tolerability/down-regulation of S1P receptors towards etrasimod for these effects. Bradycardia (including sinus bradycardia) and AV block (firs and second degree) are included as ADRs in the product information of Velsipity.

Treatment with etrasimod led to increase of mean/median systolic BP by 1 - 2 mmHg and a smaller mean/median increases of 1 mm Hg in diastolic blood compared to baseline. Hypertension-related events (combined terms) occurred at higher frequency on etrasimod compared to placebo. Hypertension is included as designated adverse drug reaction in the SmPC.

Treatment with etrasimod 2 mg was associated with changes in liver chemistry (ALT, AST, ALP, total bilirubin and gammaGT) values and total cholesterol (non-fasted) parameters. At any time on treatment with etrasimod 2 mg ALT, AST, total bilirubin, ALP and GGT were above normal range in 35%, 25%, 8.5%, 18.2% and 28.6% of patients vs. 15%, 9.2%, 4.1%, 12.7% and 11.1% of those on placebo (Placebo-controlled UC pool). In all pools, AST and/or ALT elevations > 3 × ULN were more frequent in the etrasimod 2 mg group compared to the placebo group (4.4% vs. 1.5%, respectively; Pivotal UC pool), but elevations > 5 × or 10 × ULN were similar in both treatment groups. In all pools, elevations in GGT, including elevations > 5 × ULN were more frequent in the etrasimod 2 mg group than the placebo group (3.6% vs 0.8% in pivotal UC pool). No subjects had liver chemistry elevations that met Hy's Law criteria in any treatment group in any pool.

In the Pivotal UC Pool, the median change from Baseline in total cholesterol (non-fasted) at Week 2: etrasimod 2 mg, 0.230 mmol/L (range: −3.09, 2.20) and placebo, 0.110 mmol/L (range: −2.02, 2.25) and at Week 52: etrasimod 2 mg, 0.490 mmol/L (range: −2.26, 3.26) and placebo, 0.115 mmol/L (range: −2.31, 2.31] in placebo). Median values remained within the normal range.

Increased levels of ALT and GGT and hypercholesterolemia are included as ADRs in the SmPC.

The overall rate of infections in controlled studies was comparable for etrasimod 2 mg and placebo (18.8% and 17.7%). No differences were reported for severe, opportunistic infections, herpes zoster infections, or PML. Urinary tract infection is included as a single ADR and increased risk of infections is included as warning in the SmPC.

The overall rate of TEAEs in the SOC of eye disorders was higher on etrasimod compared to placebo (4.9% vs 3.5%). Two cases of macular oedema and cystic macular oedema were reported on etrasimod 2 mg, and one case on placebo. One additional subject had TEAE PTs of Cystoid macular oedema in all Indications Pool. Macular oedema is a known class effect and it is added as ADR in the SmPC.

Malignancies occurred in 0.2% of subjects on etrasimod and 0.25% of subjects on placebo. One patient with UC had a neuroendocrine tumour with fatal outcome on etrasimod and one patient with atopic dermatitis developed a first episode of squamous cell carcinoma of the skin on placebo and several following episodes on subsequent (open-label) etrasimod treatment. Warnings of increased risk to develop malignancy is included in the SmPC.

Reductions in lymphocyte and neutrophil counts have been reported as TEAEs. Decrease in lymphocyte and neutrophil numbers is included as ADR in the SmPC.

Overall 19 cases of pregnancy (7 in the partners of male participants and 12 in the female patients) on treatment with etrasimod have been reported. Partner pregnancies (7): 2 resulted in healthy babies,

there was 1 full term birth with neonatal jaundice that resolved, 1 elective termination, 1 spontaneous abortion, and in 2 cases it was not possible to obtain any further information as consent was not given. Regarding female participant pregnancies (12): one was pre-randomisation (no etrasimod given) and one was false pregnancy. Among the remaining 10 patients, there were 2 healthy live births, 1 premature birth with neonatal jaundice and patent foramen ovale, 1 anembryonic gestation, 1 ectopic pregnancy, 1 spontaneous abortion, and 4 elective terminations/abortions.

Etrasimod has shown harmful effects on embryonal development in non-clinical studies. Similar effects are known for S1P active drugs. Therefor Etrasimod is contraindicated for pregnant women and effective contraception is required in women with child-bearing potential. This risk is also, together with other important identified and potential risks, planned to be minimised by dedicated educational material (Healthcare Professional Checklist, Patient/Caregiver Guide and Pregnancy-Specific Patient Card).

A large number of adverse events, which were reported on etrasimod, but not reported, or reported with lower frequency, on placebo, were observed in the clinical development program, e.g., arrhythmias, ischaemic heart disease, papilloedema, blurred vision, transient ischaemic attack. Causal relationship of these events with etrasimod cannot be excluded. The applicant committed to provide further long term real world safety data by means of Post-Authorisation Safety Study with the primary objective to estimate the incidence rates of safety outcomes of interest and by submitting results from the OLE for the pivotal studies 301 and 302 APD334-303. Both studies are described as category 3 study in the RMP.

3.5. Uncertainties and limitations about unfavourable effects

The key limitation of the presented program is that only a small number of older patients were exposed to etrasimod who may be at increased risk considering the known or potential cardio-vascular and other effects of etrasimod (changes in HR, AV conduction, cholesterol and BP levels, potentially related events of arrhythmias, etc.). Also, weak, or missing evidence supporting safety of drug-drug interactions against beta-blockers, Ca-channel blockers and other antiarrhythmic medications contributes to the uncertainty of data generalisability to the elderly population.

The indication covers adolescent patients aged 16 years and older. So far, only 3 patients in that age group have been exposed to etrasimod in the clinical studies presented. However, paediatric use of other S1P receptor modulators, although approved for a different indication (i.e. multiple sclerosis), provides some reassurance. Based on PK modelling, exposure of etrasimod was estimated to be 1.5 fold higher in patients with a body weight < 40 kg, which raises potential safety concerns. In the absence of clinical data in such patients, a statement to use etrasimod with caution in such patients was added in the SmpC.

Given the relatively short exposure time in the presented program, there is an uncertainty that potential risks, such as, development of malignancies might have been underestimated. Malignancy is recognised as Important potential risk in the RMP.

Patients were excluded from the studies if they had forced expiratory volume and forced vital capacity < 70% of predicted values. SmPC recommends, that etrasimod is used with caution in the patients with severe respiratory disease (e.g., pulmonary fibrosis, asthma, and chronic obstructive pulmonary disease), as reductions in these parameters were observed in patients treated with S1P receptor modulators. Data suggest that etrasimod had no effect on these parameters.

The role of the metabolites M3 and M6, which may be major human metabolites, with regards to their potential impact on QT interval is going to be further elucidated by the applicant by a recommended in-vitro study. Appropriate warning statements are included in the SmPC.

Long-term consequences of ADRs such as hypercholesterolemia and Hypertension, as well as impact on hepatic parameters is unclear. Limited evidence is available in relation with potential risks of long-term use of etrasimod (e.g., risk of development of serious infections, malignancy). Appropriate information is given in the SmpC.

The size and the setting (use of concomitant treatments, other confounding factors) of the current safety information may be inadequate to fully identify potential signals, including potential important risks (e.g., PRES, PML).

The applicant committed to provide further long term real world safety data in the target population, including the potentially important AEs by means of Post-Authorisation Safety Study with the primary objective to estimate the incidence rates of safety outcomes of interest and by submitting results from the OLE for the pivotal studies 301 and 302 APD334-303. Both studies are described as category 3 study in the RMP.

3.6. Effects Table

Table 67: Effects Table for etrasimod (studies 302 and 301)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Clinical remission week 12	SF subscore 0 (or 1 with an at least 1 point improvement), RB subscore 0, and ES ≤ 1 (excluding friability)	% (pooled)	26.0	10.9	Two studies with consistent results (one with p<0.001, and one with p=0.026). Strong evidence. Composite endpoint requested as secondary in CHMP UC guideline only	Studies APD334-301 and 302
Clinical remission week 52	See above	%	32.1	6.7	One study only, p<0.001; evidence sufficiently strong	Study APD334-301
Symptomatic remission week 12	SF subscore = 0 (or = 1 with a ≥ 1 point decrease from Baseline) and RB subscore = 0.	% (pooled)	46.4%	25.1%	Two studies with consistent results (one with p<0.001, and one with p=0.001). Strong evidence. EP consistent with the co-primary EPs requested by CHMP UC guideline	Studies APD334-301 and 302
Symptomatic remission week 52	See above	%	43.4	18.5	One study only, p<0.001; evidence sufficiently strong	Study APD334-301

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Mucosal healing at week 12	ES ≤ 1 (excluding friability) with histologic remission measured by a Geboes Index score < 2.0.	% (pooled)	19.0	6.5	Two studies with consistent results (one with p<0.001, and one with p=0.036). Strong evidence. EP consistent with the co-primary EPs requested by CHMP UC guideline	Studies APD334-301 and 302
Mucosal healing at week 52	See above	%	26.6	8.1	One study only, p<0.001; evidence sufficiently strong	Study APD334-301
Endoscopic Improvement at week 12	Endoscopic score ≤ 1.	% (pooled)	33.1	16.2	Two studies with consistent results (one with p<0.001, and one with p=0.009). Strong evidence. Composite endpoint requested as secondary in CHMP UC guideline only	Studies APD334-301 and 302
Endoscopic normalisation at week 12	ES=0	%	Study 301: 14.6 Study 302: 17.1	Study 301: 4.4 Study 302: 8.0	Two studies with consistent results (one with p<0.002, one with p=0.009	Studies APD334-301 and 302
Corticosteroid free clinical remission Week 52	SF subscore = 0 (or = 1 with a ≥ 1-point decrease from Baseline), RB subscore = 0, ES ≤ 1, and have not received corticosteroids for ≥ 12 weeks in the 40-Week Treatment Period	%	32.1	6.7	One study only, p<0.001; evidence sufficiently strong.	Study APD334-301
Corticosteroid-free endoscopic improvement week 52	subjects with an ES ≤ 1 (excluding friability) and corticosteroid-free for ≥ 12 weeks immediately prior to Week 52	%	36.9	10.4	One study only, p<0.001; evidence sufficiently strong. EP not fully compliant with one of the two co-primary EPs as requested by the CHMP UC guideline.	Study APD334-301

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Corticosteroid free symptomatic remission	SF subscore = 0 (or = 1 with a ≥ 1 point decrease from Baseline) and RB subscore = 0 and corticosteroid-free for ≥ 12 weeks immediately prior to Week 52	%	43.4	18.5	One study only, p<0.001; evidence sufficiently strong. Endpoint consistent with one of the two co-primary EPs as requested by the CHMP UC guideline.	Study APD334-301
Sustained clinical remission	SF subscore = 0 (or = 1 with a ≥ 1-point decrease from Baseline), RB subscore = 0, and ES ≤ 1 (excluding friability) at both Week 12 and Week 52.	%	17.9	2.2	One study only, p<0.001; evidence sufficiently strong	Study APD334-301
Unfavourable Effects						
Elevations of liver enzymes	ALT > 3 × ULN GGT > 5 x ULN	%	4.4 3.6	1.5 0.8	Consistent across all analyses pools. Sufficiently strong evidence	Pivotal pool
Bradycardia	TEAE	%	1.0	0	Consistent across all analyses pools. Class effects. Sufficiently strong evidence	Placebo-controlled pool
AV block first and second degree	TEAE	%	0.6	0	Consistent across all analyses pools. Class effects. Sufficiently strong evidence	Placebo-controlled pool
Hypertension	Median change	mmHg	2	0	Placebo-controlled setting. Class effect. Sufficiently strong evidence	Placebo-controlled pool
Macular oedema	TEAE	%	0.3	0.3	Additional case of Cystoid macular oedema reported in OL setting on etrasimod 2 mg. Increase in central foveal thickness observed. Sufficiently strong evidence	Placebo-controlled pool
Central foveal thickness	Increase in central foveal Thickness by > 40 µm at Week 52	%	15.2	3.8	Placebo-controlled setting. Known class effect. Strong evidence.	Placebo-controlled pool
Urinary tract infection	TEAE	%	2.1	1.0	Placebo-controlled setting. Small difference to placebo. Weak evidence.	Placebo-controlled pool

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Malignancies	TEAE	%	0.2	0.3	Not adequately controlled setting. Short observation time. Weak evidence	All indications pool

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Efficacy

The target population, at the time of inclusion into the study was suffering from moderate to severe disease with both a relevant burden of symptoms, as well as a relevant mucosal inflammation, which is deemed the relevant predictor of long-term outcomes. The studies have therefore put the focus on documenting the improvement and resolution of the two main symptoms in UC, rectal bleeding (RB) and stool frequency (SF), on the mucosal healing, as well as into a composite evaluation of these two aspects.

It has been demonstrated that – within a relatively short period of 12 weeks – the substance was inducing relevant reduction of both, the symptoms, as well as of the mucosal inflammation made visible by endoscopy. More than 25% of the patients achieved the combined clinical remission endpoint, while patients on placebo only could achieve this in just above 10%, indicating a clinically relevant gain over placebo treatment. When dividing this into a symptomatic remission endpoint, it can be shown that almost 50% of the patients have normal or near normal symptomatology (while only 25% can achieve this with placebo) which is considered highly clinically relevant. On the other hand, after 12 weeks not even 20% of the patients have normal mucosal surface in the colon, indicating that in the vast majority of patients, inflammation is ongoing at this early time-point. However, placebo treated patients only achieve this by 6.5% and thus this gain in effect also needs to be considered clinically relevant.

The results of the week 52 evaluation of the study 301, as well as the combined evaluation of week 12 and week 52 endpoints, demonstrated that the effects achieved early at twelve weeks, can be maintained over the course of a whole year, which is considered relevant both on an individual basis for the patients, as well as with regard to the further considerations on additional and/or switch of treatments. After one year, still 43% of the patients had no or no relevant symptoms, and more than 37% had an improved state of the mucosa, as compared to the time of inclusion. Those kept in a state of full mucosal healing is 26.6%, indicating that more than 25% of the patients can be expecting clinical benefit in the long-term, with avoiding repeated exacerbations, and complications, as well as colon surgery.

On the other hand, an improvement of the long-term prognosis was not achieved in 75% (which is the counterfact of those having mucosal healing) of the patients. However, this needs to be seen on the background of reports for other substances in the therapeutic indication for which an initial rate of non-response is given, ranging from 20-60%, and for which an additional 20% lose response in the long-term. Considering the overall rate of more than 40% symptomatic remission, the achieved 25% long-term mucosal healing rate appears to be within the range previously reported. Since most or even all of the most recent developments have conducted different studies, in which only primary responders were included (contrary to the study 301 presented in this application which was following up patients

irrespective of their primary response), a comparison of the magnitude of effects is difficult to undertake. Such compounds achieved mucosal healing rates of 50%-60% after maintenance treatment of 52 weeks. However, a relevant proportion of the patients in such programmes did not achieve clinical response after induction treatment and can therefore be assumed to not having been included in this maintenance study.

Therefore, the rate of 25% mucosal healing after 12 months of treatment does not appear to be smaller than with other therapies in the field.

There are some uncertainties on the interpretation of the data, mainly due to the chosen study design, the subsequent high rates of occurrence of intercurrent events, the related problems of defining an appropriate estimand, and an accurate method for missing data imputation, as well as with regard to the included patient population (MMS 4 patients, patients on 5-ASA only). However, the conducted sensitivity analyses did not question the overall results, and the chosen primary evaluation for the primary, as well as most secondary endpoints is generally not put into question. Therefore, the remaining uncertainties with regard to effect size are regarded to be minor.

Safety:

Overall, frequency of TEAEs on etrasimod, predominantly mild or moderate severity, and low drop-out rates due to TEAEs suggest an acceptable safety profile. The established ADRs lymphopenia, neutropenia, hypertension, bradycardia, AV block (first and second degree), increased ALT/AST and GGT, headache, dizziness, urinary tract infection, macular oedema, are in line with the mechanism of action of etrasimod and with the known class effects of S1P substances. All of them are appropriately labelled in the product information.

Uncertainties remain with regards to the potential effects of the M3 and M6 metabolites on QT interval and will be addressed in the post-approval phase by conducting in-vitro investigations as recommended to the applicant.

Safety data on etrasimod are limited in elderly patients and subjects with relevant concomitant diseases (cardiovascular, pulmonary, infections, malignancies, etc.), as well as in adolescents. However, there are no safety concerns that would prohibit the use of etrasimod in these age groups and the safety database will be broadened post-authorisation by the data from two category 3 studies.

Overall, it should be noted, that the lack of data in some patient populations is adequately reflected in the SmPC, i.e., etrasimod treatment is not recommended in patients.

- With immunodeficient state.
- 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.
- Who have Severe active infections, active chronic infections.
- Active malignancies.
- Severe hepatic impairment
- During pregnancy and in women of childbearing potential not using effective contraception.

Risk minimisation measures in patients with cardiac conditions, or at risk of developing macular oedema including a targeted educational package (Healthcare Professional Checklist, Patient/Caregiver

Guide and Pregnancy-Specific Patient Card) are being implemented and are considered acceptable (see Chapter 4). Use of etrasimod in the patients with severe hepatic impairment is not recommended due to the potential risk of QT prolongation. In patients with a weight < 40 kg, etrasimod should be used with caution as labelled in the product information.

Overall, the safety profile of etrasimod is considered acceptable.

3.7.2. Balance of benefits and risks

The substance etrasimod has been presented with a programme adequately documenting overall efficacy in the treatment of moderate to severe ulcerative colitis. The substance is considered to be a valuable contribution to the potential treatment armamentarium in the disease, which for all available treatments have relatively low overall rates of achieving and maintaining a satisfactory rate of clinical, symptomatic, and endoscopic remission.

The evidence for the beneficial effects of the compound is sufficiently strong, and the results achieved are in line with results achieved with other compounds in the field, or with similar mechanism of action. Similar to the other products in this class of medicines licensed for UC, the use of the etrasimod will be indicated in patients failing on either conventional, or more recently, either biologic, or JAK-inhibition based treatment modalities, and in a moderately to severely disease population. This is considered justified on the basis of the known mechanism of action and adverse effects.

The compound displayed adverse effects known for this class of medicines, such as the heart rate reduction at initial dosing, which prevents patients with relevant cardiovascular disease being treated and which can potentially cause further HR related adverse effects, such as syncope. Also the immunosuppressive properties of the agent preventing treatment in certain at risk populations, or causing relevant infectious, potentially serious and even life-threatening, need to be mentioned as a disadvantage. Nevertheless, it is considered that the safety profile of etrasimod is manageable with the implemented risk minimisation measures and that the treating physicians will be able to follow the absolute and relative contraindications and to handle the adverse effects of the compound appropriately.

The demonstrated efficacy of etrasimod in patients ≥ 16 years of age with moderate to severely active ulcerative colitis are considered to outweigh the identified and potential risks.

3.8. Conclusions

The overall benefit/risk balance of Velsipity is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Velsipity is favourable in the following indication:

Velsipity is indicated for the treatment of patients 16 years of age and older with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy, or a biological agent.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following

conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency.
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **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 Velsipity:

- An electrocardiogram (ECG) should be obtained in all patients to assess for pre-existing cardiac abnormalities.
- Velsipity 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 Velsipity in patients taking medicines known to decrease heart rate.
- Velsipity 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.
  - Velsipity should not be used in patients with an absolute lymphocyte count < 0.2 x 10^9/L.
- Recent transaminase and bilirubin levels should be available.
  - Velsipity 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.
- Velsipity must not be used during pregnancy or in women of childbearing potential not using effective contraception.
- An ophthalmic evaluation of the fundus, including the macula, is recommended in all patients.
  - Patients with a macula oedema should not use Velsipity.

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.
- 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.
- The use of live attenuated vaccine should be avoided for at least 2 weeks after discontinuation of treatment with Velsipity.
- Hepatic enzymes should be monitored at months 1, 3, 6, 9, and 12 on therapy and periodically thereafter. Velsipity 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 Velsipity. Pregnancy testing should be repeated regularly. If a woman becomes pregnant during treatment, Velsipity must be immediately discontinued.
- Patients with a history of diabetes mellitus, uveitis, 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.
- Patients should be cautioned against exposure to sunlight without protection to prevent 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 Velsipity should be discontinued if PRES is suspected.

Patient/Caregiver Guide

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

- Velsipity 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 Velsipity, 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 Velsipity 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 Velsipity. 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 Velsipity.
- 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.
- Velsipity 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 with Velsipity.
  - Women of childbearing potential must have a negative pregnancy test before treatment initiation with Velsipity. Patients should tell their doctors straight away if they become pregnant while taking Velsipity. 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:

- Velsipity 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, Velsipity must be immediately discontinued, and follow-up examinations should be performed.

These conditions reflect the advice received from the PRAC.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that etrasimod is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.