25 March 2021
EMA/CHMP/206970/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ponvory

International non-proprietary name: ponesimod

Procedure No. EMEA/H/C/005163/0000

Note

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

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Table of contents

List of abbreviations

ACT-128800	Ponesimod
ADEM	Acute Disseminated Encephalomyelitis
AE	Adverse Events
AESI	Adverse Events of Special Interest
AIA	Adjuvant-Induced Arthritis
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ANOVA	Analysis of Variance
APTT	Activated Partial Thromboplastin Time
ARR	Annualised Relapse Rate
AUC	Area Under the concentration-time Curve
AUC_{inf}	Area Under the concentration-time Curve from time 0 to infinity with extrapolation of the terminal phase
AUC_{0-24}	Area Under the concentration-time Curve in a dosing interval of 24 hours
AUC_{0-t}	Area Under the concentration-time Curve from time 0 to the last measurable concentration
AUC_{τ}	Area Under the concentration-time Curve during a dose interval (τ)
AVB	Atrioventricular Block
BAFF	B cell-Activating Factor
BCRP	Breast Cancer Resistance Protein
BID	*Bis In Die:* twice a day
BP	Blood Pressure
B/R	Benefit / Risk
BW	Body Weight
cAMP	Cyclin Adenosine Monophosphate
CBC	Complete Blood Count
CDA	Confirmed Disability Accumulation
CFA	Complete Freund's Adjuvant
CFU	Colony-Forming Unit
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese Hamster Ovary
CIs	Confidence Intervals
CM	Cryptococcal Meningitis
C_{max}	Maximum Observed Plasma Concentration
CNS	Central Nervous System
CQA	Critical quality attribute
CRP	C-Reactive Protein
C_{trough}	Trough plasma concentration
$C_{trough,ss}$	Trough plasma concentration at steady-state
CUAL	Combined Unique Active Lesions
CV	Coefficient of Variation
DB	Double-Blind
DBP	Diastolic Blood Pressure
DDI	Drug-Drug Interactions
DMT	Disease-Modifying Therapies
DNFB	Dinitrofluorobenzene
DoE	Design of experiments
DRF	Dose Range Finding
DSC	Differential scanning calorimetry
EAE	Experimental Autoimmune Encephalomyelitis
EC	European Commission
EC_{50}	Half maximal effective concentration
eCRF	Electronic Case Report form
ECG	Electrocardiogram
ECHO	Echocardiograph
EFD	Embryo-Fetal Development
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
EOS	End Of Study
EOT	End Of Treatment
E-R	Exposure-Response
ERA	Environmental Risk Assessment

Erk1/2	Extracellular signal-Regulated Kinase 1/2
ESR	Erythrocyte Sedimentation Rate
ETA	Endothelin receptor Type A
EU	European Union
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume in 1 second
Fpen	Factor of market penetration
FS	Functional Systems
FSIQ–RMS	Fatigue Symptom and Impact Questionnaire-Relapsing Multiple Sclerosis
FVC	Forced Vital Capacity
FAS	Full Analysis Set
FU	Follow-up
GC	Gas chromatography
GCP	Good Clinical Practice
Gd+	Gadolinium enhancing
GLP	Good Laboratory Practices
GRO/KC	human Growth-Regulated Oncogene/ Keratinocyte Chemoattractant
GTP	Guanosine Triphosphate
GVS	Gravimetric vapour sorption
hERG	human ether-à-go-go related gene
HPLC	High-performance liquid chromatography
HR	Heart Rate, Hazard Ratio
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
IC_{20}	20% inhibitory concentration
IC_{50}	half-maximal inhibitory concentration
LC-MS/MS	Liquid Chromatography coupled to Mass Spectrometry
LS	Least Squares
LSC	Liquid Scintillation Counting
IL	Interleukin
IFN	Interferon
LPA	Lysophosphatidic Acid Receptors
MAA	Marketing Authorisation Application
MAH	Marketing authorisation holder
MAIC	Matching-Adjusted Indirect Comparison
MAO	Monoamine Oxidase
MAR	Missing At Random
MATE	Multidrug and Toxic Compound Extrusion
MBMA	Model-Based Meta-Analysis
MCP-1	Monocyte Chemoattractant Protein-1
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MIP-1α	Macrophage Inflammatory Protein-1 alpha
MMRM	Mixed-effect Model Repeated Measurements
MOG	Myelin Oligodendrocyte Glycoprotein
MRI	Magnetic Resonance Imaging
mRNA	messenger Ribonucleic Acid
MS	Multiple Sclerosis
MTD	Maximum Tolerated Dose
NB	Negative Binomial
NEDA	No Evidence of Disease Activity
NK	Natural Killer
NKT	Natural Killer T
NMR	Nuclear magnetic resonance
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
OATP	Organic Anion Transporting Polypeptide
OCT	Organic Cation Transporter
OECD	Organisation for Economic Co-operation and Development
OSB	Ophthalmology Safety Board
QC	Quality Control
QD	Once a day

QTcF	QT corrected using Fridericia's formula
QTcI	individually corrected QT
ΔΔQTcI	placebo-corrected change from baseline in the
PAM	Post-Authorisation Measure
PAR	Proven acceptable range
PBRER	Periodic Benefit-Risk Evaluation Report
PBT	Persistence, Bioaccumulation and Toxicity
PEC_{sw}	Predicted Environmental Concentrations surfacewater
PEF	Peak Expiratory Flow
PD	Pharmacodynamic, Protocol Deviation
PDE	Permitted daily exposure
P-gp	P-glycoprotein
PFT	Pulmonary Function Tests
PGI-S	Patient Global Impression of Severity
Ph. Eur.	European Pharmacopoeia
PIF	Peak Inspiratory Flow
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PL	Package Leaflet
PLGF2	Placental Growth Factor
PML	Progressive Multifocal Leukoencephalopathy
popPK	Population pharmacokinetic
PPS	Per-Protocol analysis set
PPND	Pre- Postnatal Developmental
POEM	Pregnancy Outcomes Enhanced Monitoring
PRAC	Pharmacovigilance Risk Assessment Committee
PRES	Posterior Reversible Encephalopathy Syndrome
PRO	Patient-Reported Outcome
PT	Prothrombin Time, Preferred Term
PUVA	Psoralen and Ultraviolet A
QTPP	Quality target product profile
Rac1	Ras-related C3 botulinum toxin substrate 1
RANKL	Receptor Activator of Nuclear factor Kappa-B Ligand
RANTES	Regulated upon Activation, Normal T Cell Expressed and Presumably Secreted
RBC	Red Blood Cell
RDST	Repeated Dose Toxicity Studies
RH	Relative humidity
RMS	Relapsing forms of Multiple Sclerosis
RRMS	Relapsing Remitting Multiple Sclerosis
RWG	Resonant Waveguide Grating
SA	Scientific Advice
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SLE	Systemic Lupus Erythematosus
SmPC	Summary of Product Characteristics
SOC	System Organ Classes
SPMS	Secondary Progressive Multiple Sclerosis
SRBC	Sheep Erythrocytes
S1P	Sphingosine 1-Phosphate receptor
$S1P_1$	Sphingosine 1-phosphate receptor 1
$S1P_2$	Sphingosine 1-phosphate receptor 2
$S1P_3$	Sphingosine 1-phosphate receptor 3
$S1P_4$	Sphingosine 1-phosphate receptor 4
$S1P_5$	Sphingosine 1-phosphate receptor 5
TDAR	T-Dependent Antibody Response
TEAEs	Treatment-Emergent Adverse Events
TEMSO	Teriflunomide Multiple Sclerosis Oral
t_{max}	Time at maximum plasma concentration
$t_{1/2}$	Elimination half-life
TP	Treatment Period
TFUQ	Targeted Follow-Up Questionnaire
TGA	Thermogravimetric analysis
TSE	Transmissible spongiform encephalopathy

UGT	Uridine Diphosphate Glucuronosyltransferases
ULQC	Upper Limit of Quantification
ULN	Upper Lower Normal
UV	Ultraviolet
UVB	Ultraviolet B
Vd	(Apparent) Volume of distribution
Vd_{ss}	Volume of Distribution at Steady State
VZV	Varicella Zoster Virus
WBC	White-Blood Counts
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Janssen-Cilag International N.V. submitted on 2 March 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Ponvory, through the centralised procedure falling within the Article 3(1) and point 3of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 20 September 2018.

The applicant applied for the following indication treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features.

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).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0128/2018 on the agreement of a paediatric investigation plan (PIP). At the time of submission of the application, the PIP P/0128/2018 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

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.

Applicant's request(s) for consideration

New active Substance status

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

Scientific advice

The applicant received the following Scientific Advice (SA) on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
22 September 2011	EMEA/H/SA/2170/2/2011/II EMEA/H/SA/2170/1/2011/III	Fernando de Andrés Trelles Christine Gispen-de Wied
24 July 2014	EMEA/H/SA/2170/4/2014/II EMA/H/SA/2170/FU/1/2014/III	Susan Morgan Marion Haberkamp
31 May 2018	EMEA/H/SA/2170/1/FU/2/2018/I EMEA/H/SA/2170/4/FU/1/2018/II	Susan Morgan Marion Haberkamp
28 February 2019	EMA/H/SA/2170/4/FU/2/2019/I EMEA/H/SA/2170/4/FU/2/2019/II	Fernando de Andrés Trelles Marion Haberkamp

EMEA/H/SA/2170/2/2011/II pertains to clinical aspects, specifically study design and primary endpoint for a trial to test efficacy, safety and tolerability of ponesimod in patients with clinically isolated syndrome.

EMEA/H/SA/2170/1/2011/III pertains to non-clinical and clinical aspects for studies on clinically isolated syndrome and RMS:

- Regarding the non-clinical aspects, it was agreed that the non-clinical package was rather complete, but it was recommended to justify the absence of secondary pharmacology studies and to further evaluate toxicity including reproductive toxicity. The applicant was informed that an environmental risk assessment (ERA) would be needed to be available before marketing authorisation application (MAA). Additionally, the development drug plans for a combination with other DMT were discouraged.
- Regarding the pharmacological and clinical aspects, the approach to dose finding was agreed but it was recommended to further address the potential drug-drug interactions for ponesimod. With regards to the clinical studies, the following aspects of the study design were discussed: superiority study versus Avonex/placebo, an open-label rater blinded design, primary (annualised relapse rate [ARR] versus time to first relapse) and secondary endpoints (hierarchical order and fatigue scale), pooled analysis for disability. The use of placebo, time-to-event primary endpoint and the open-label rater-blinded assessment were not discouraged. It was recommended to further discuss the hierarchical order of secondary endpoints. With regards to fatigue, the applicant was informed that an effect on fatigue could be claimed provided the effect is apart from statistically significant, also clinically significant. Further advice was given on safety (lymphocyte counts monitoring).

EMEA/H/SA/2170/4/2014/II pertains to clinical aspects in relation to an add on indication for relapsing forms of MS who have active disease despite treatment with dimethyl fumarate. This SA is not relevant for this MAA.

EMA/H/SA/2170/FU/1/2014/III pertains to non-clinical and clinical aspects.

- The non-clinical aspects were related to the add on indication and therefore, not relevant for this MAA.
- Regarding clinical aspects, the applicant presented a modified drug development plan including teriflunomide 14 mg as active comparator which was found acceptable. Regarding the study population, the applicant was advised to include sufficient patients with low and highly active RRMS in case the benefit risk (B/R) can only be considered positive for the later. The inclusion of subjects with SPMS with superimposed relapses was discouraged as it might complicate trial design and hamper the interpretation of the effect on disability, although it was agreed that an effect on relapses can be extrapolated from RRMS to SPMS based on the same underlying pathophysiology i.e. inflammatory process. The applicant was advised to include disability progression as the main secondary endpoint in line with the Guideline on Clinical Investigation of Medicinal Products for the

Treatment of Multiple Sclerosis (EMA/CHMP/77185/2011, Rev 2) and therefore invited to revise the hierarchical order. Further recommendations were given for statistical methods including regression models, sensitivity analyses, subgroup analyses and sample size. Moreover, the applicant received advice about requirements/recommendations in the context of MAA based on one pivotal trial (CPMP/EWP/2330/99) including the level of significance (e.g. 2-sided $p<0.01$) but also the need for internal consistency (similar effects in sub-populations), high trial quality. With regards to dose selection is phase 3 studies, it was agreed that the 20 mg dose is the chosen dose for phase 3 based on a reduced tolerability with the 40 mg dose but the applicant was invited to evaluate whether a dose of 30 mg would provide potential benefit for disease progression over the 20 mg while remaining safe. Finally, the safety monitoring plan was discussed, and it was recommended to further justify the use of an up-titration scheme in phase 3 in relation to the dose escalation in phase 2 trials.

EMEA/H/SA/2170/1/FU/2/2018/I pertains to a single quality question on the suitability of the two starting materials.

EMEA/H/SA/2170/1/FU/2/2018/II pertains to a single clinical question on the suitability of the proposed revision of the secondary endpoints and multiplicity testing strategy while the study was going. The proposed revision placed the endpoint "*time to 12-week confirmed disability accumulation (CDA) from baseline to end of study (EOS)*", previously the first endpoint at the end of a new strategy including the "*change from baseline to Week 108 in fatigue-related symptoms as measured by the symptoms domain of the Fatigue Symptom and Impact Questionnaire-Relapsing Multiple Sclerosis (FSIQ–RMS)*" and "*cumulative number of combined unique active lesions (CUAL) from baseline to Week 108*" as first and second endpoints, respectively. Given that the proposed changes are motivated by results seen in other studies and not by data collected in the ongoing study, the applicant's claim that data collected remain fully blinded to the sponsor and that the measures of disability remained, the new strategy was considered acceptable. However, it was recommended to switch the secondary endpoint "*Time to 12-week CDA from baseline up to EOS*" with the exploratory endpoint "*Time to first 24-week CDA from baseline up to EOS*". It was also advised that positioning disability progression in hierarchy order is not in line with the Committee for Medicinal Products for Human Use (CHMP) guideline on clinical investigation of medicinal products for the treatment of Multiple Sclerosis (EMA/CHMP/771815/2011, Rev. 2) that states that disability progression should be considered the key secondary endpoint (if not the first one). Even if at the time of submission for a MAA all endpoints will be assessed regardless of statistical significance or order of testing, it was noted that the new hierarchical strategy would only allow to test CDA at the full alpha level if the other two secondary endpoints were successful.

EMA/H/SA/2170/4/FU/2/2019/I pertains to a single quality question on the suitability of the starter pack design consisting of nine different dose strengths with different tablet sizes and different colours to be administered over the 14-day period.

EMA/H/SA/2170/4/FU/2/2019/II pertains to clinical aspects including (i) cardiac monitoring in ongoing studies; (ii) expected B/R supporting the intended MAA indication (patients with RMS); (iii) statistical analysis plan (SAP) for Study B301; (iv) secondary endpoint analysis; and (v) pooling strategy for ponesimod safety data:

- It was considered that further data sustaining a "better safety profile" compared to a non-selective S1P modulator was needed prior to lift the requirement for first-dose monitoring in patients without risk factors and to reduce the duration of first dose monitoring in those with risk factors for symptomatic bradycardia or heart block.
- It was noted that that a positive B/R will need to be demonstrated across the disease activity spectrum, including patients with SPMS and overlapping relapses. The recommendation of including

enough patients with low and high level of activity (EMEA/H/SA/2170/1/FU1/2014/III) was reiterated.

- Aspects of the study design were further discussed. The CHMP was in agreement with the evaluation of the primary endpoint in B301, with the caveat that missing data imputation should target a full treatment policy strategy rather than a partial one. Regarding the testing of the primary null hypothesis and the change proposed by the applicant "*the primary null hypothesis was to be tested at a two-sided 1% alpha level for conclusive evidence and 5% for a positive study*", the CHMP stated that the previously agreed (EMA/CHMP/SAWP/429513/2014) level of significance of 1% would be required to justify the use of a single pivotal study.
- It was noted that recommendation on the secondary endpoints and hierarchical order were only partially implemented because 24-week CDA was included as a secondary endpoint after the 12-week CDA (#4rank). Recommendations were given to handle the potential bias due to informed censoring with regards to time to CDA endpoints.
- The applicant´s proposal to characterise the safety profile of in a pool safety set in RMS was agreed.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Elita Poplavska

The application was received by the EMA on	2 March 2020
The procedure started on	26 March 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	15 June 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	15 June 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	29 June 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	23 July 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	17 November 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	04 January 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	14 January 2021
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	28 January 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	22 February 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	11 March 2021
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 Ponvory on	25 March 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The claimed indication is treatment of adult patients with RMS with active disease defined by clinical or imaging features.

Multiple sclerosis (MS) is an inflammatory immune-mediated and neurodegenerative disorder of the central nervous system (CNS). This disease is characterised by a heterogeneous clinical expression, an unpredictable course, and a variable prognosis. MS is characterised by inflammation, demyelination, neuronal and oligodendrocyte loss, and disruption of the blood-brain barrier, leading to irreversible deficits in physical function and cognition and an impaired quality of life.

2.1.2. Epidemiology

The estimated number of people with MS increased was 2.8 million in 2013 worldwide. (MS International Federation, 2020). In Europe, the median prevalence is 133 cases per 100,000, and the highest prevalence of MS occurs in countries with higher latitudes, including Sweden (218 per 100,000), Denmark (282 per 100,000) and Germany (303 per 100,000).

MS is usually diagnosed during early adulthood, with an average age of onset of 32 years. MS is twice as common among women than men.

2.1.3. Aetiology and pathogenesis

Although the aetiology of MS is still unknown, it is widely accepted that it is an immune-mediated process triggered by only partially understood environmental factors in genetically susceptible people.

MS results from a cascade of events involving activation of both adaptive and innate immune system, both acute focal and diffuse chronic inflammation, demyelination, culminating in neuroaxonal loss in the CNS, namely retina, spinal cord and brain.

2.1.4. Clinical presentation, diagnosis and prognosis

The two main clinical features of MS are exacerbations (also called attacks or relapses) and chronic, progressive loss of neurological function. Relapses are considered the clinical expression of acute, inflammatory and demyelinating, focal lesions of the CNS which leads to the slowing or blockade of axonal conduction at diverse affected sites of the CNS. After the acute phase, permanent disability as clinical sequalae represents irreversible neuro-axonal injury due to focal inflammation. In MS, progression in neuronal disability is due to accumulation of neuro-axonal injury either due to focal inflammation or due to diffuse chronic neuroinflammation

Relapsing-remitting MS (RRMS) is the most common form of MS, representing approximately 85% of patients at diagnosis. According to earlier natural history studies, approximately 50% of patients with RRMS will, within the first 20 years after diagnosis, develop secondary progressive MS (SPMS), which is characterised by worsening disability independently of the presence or absence of relapses. Recent findings from cohorts of patients mostly treated with DMTs from early onset have found lower transition

rates to SPMS. Additionally, primary progressive MS is the presenting form at diagnosis in approximately 15% of MS patients and is characterised by chronic worsening of disability early in the disease and in the absence of relapses

The evaluation of suspected MS begins with a detailed clinical history and examination. According to MS International Federation,2013 MS Atlas, the most common presenting symptoms were found to be sensory (40%), and motor (39%), and the least common were pain (15%) and cognitive issues (10%). The widely used McDonald diagnostic criteria have been developed to facilitate earlier diagnosis and initiation of treatment. Magnetic Resonance Imaging (MRI) and cerebrospinal fluid findings can be utilised to support clinical diagnostic criteria for MS.

No prognostic indicators are established as reliable, and accurate prediction of outcome for an individual patient.

2.1.5. Management

There is no cure available for MS. Therapies for MS include treatment for relapses (e.g. steroids), symptomatic treatments (e.g. drugs for fatigue and pain) and those that alter the course of the disease (disease-modifying therapies [DMTs]).

There are currently several approved DMTs in MS with different efficacy and safety profiles.

The injectable interferons (IFN) (interferons β-1a and β-1b) and glatiramer acetate have a well-established efficacy and safety profile. The safety profile for the IFNs includes depression and risk of suicide, hepatic injury, decreased peripheral blood count, anaphylaxis, and injection-site reactions. For glatiramer acetate, safety concerns include immediate post-injection reactions/necrosis and transient chest pain.

The safety profile of approved sphingosine 1-phosphate receptor (S1P) modulators fingolimod, siponimod and ozanimod includes cardiac effects at initiation of treatment (bradyarrhythmia and atrioventricular [AV] block) and QT prolongation, infections including progressive multifocal leukoencephalopathy (PML), respiratory effects, increased liver enzymes and blood pressure and malignancies. Due to these safety issues, the first approved oral nonselective S1P receptor modulator fingolimod was indicated for RRMS patients with highly active disease despite a previous DMT or for rapidly evolving, severe MS.

Dimethyl fumarate and teriflunomide are oral agents that have demonstrated moderate efficacy in the treatment of RRMS. The safety profile of dimethyl fumarate includes gastrointestinal adverse events (AEs), flushing, lymphopenia, infections including PML, liver injury. The safety profile for teriflunomide includes hepatotoxicity, bone marrow suppression, peripheral neuropathy, increased blood pressure, interstitial lung disease, hypersensitivity and serious skin reactions and teratogenicity. These agents also have slow pharmacokinetics (PK)/pharmacodynamic (PD) reversibility and high propensity for drug-drug interactions (DDIs) as well as complexities related to metabolism (requiring genotyping).

Cladribine is a highly effective oral treatment for RRMS patients with highly active disease. The safety profile includes prolonged lymphocyte count reduction, infections including potential reactivation of tuberculosis, HIV, hepatitis B and malignancies.

Natalizumab was the first monoclonal antibody DMT approved for highly active RRMS. The safety profile includes PML, herpes encephalitis, meningitis and acute retinal necrosis, hepatotoxicity, and serious hypersensitivity reactions.

Alemtuzumab is a highly effective monoclonal therapy originally indicated for RRMS patients with active disease. The safety profile of alemtuzumab includes infusion-related reactions, infections, autoimmune

disorders including immune thrombocytopenia, nephropathies and thyroid disorders, stroke and increased risk of malignancy.

Ocrelizumab, another highly effective monoclonal DMT administered intravenously, is also indicated for RRMS patients with active disease, as well as early primary progressive MS. The safety profile of ocrelizumab includes infusion-related reactions and infections including PML, herpes and hepatitis B reactivation; an increased risk for malignancies, may exist. Ofatumumab, another anti-CD20 monoclonal DMT administered subcutaneously, is indicated for active RMS. The safety profile of ofatumumab includes injection-related reactions and infections.

Appropriate treatment is selected on an individual patient basis, depending on patient and disease characteristics and the drug-profile, including mechanisms of action, risk profile, and monitoring requirements. Despite the availability of a number of medications for the treatment of MS, there remains a need for an effective oral agent with a favourable safety and tolerability profile.

About the product

Ponesimod (JNJ-67896153/ACT-128800), is an iminothiazolidinone derivative, and is an orally active, selective modulator of the sphingosine 1-phosphate receptor 1 ($S1P_1$). It binds with high affinity to $S1P_1$ receptors located on lymphocytes and in other cell types, e.g. cardiomyocytes. Ponesimod blocks the capacity of lymphocytes to egress from lymph nodes reducing the number of lymphocytes in peripheral blood.

Ponesimod is proposed to be used in the treatment of adult patients with RMS with active disease defined by clinical or imaging features. It is formulated as film-coated tablets to be dosed orally at a dose 20 mg once daily, following a gradual 14-day up-titration regimen starting with 2 mg.

Type of Application and aspects on development

The legal basis is Article 8.3 of Directive 2001/83/EC - complete and independent application

The applicant sought SA on several occasions during the development of ponesimod. The SA pertained to the following quality, non-clinical, and clinical aspect as summarised above. Regarding quality aspects, the recommendations received concerning the starting materials have been followed by the applicant. The non-clinical development programme has been conducted in compliance with the respective EMA/ICH guidelines and recommendations received have been also largely followed by the applicant. With regard to the clinical development programme, the provided SA were not fully followed, most importantly the advice regarding the testing hierarchy of secondary endpoints, positioning disability progression in the testing hierarchy first after relapse rate, was not followed.

The applicant had MAA pre-submission meetings with the Co-Rapporteur (Latvia, State Agency of Medicines) and the Rapporteur (The Netherlands, Medicines Evaluation Board) on 23 September 2019 and 25 September 2019, respectively.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as immediate release film-coated tablet containing 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg or 20 mg of ponesimod as active substance.

Other ingredients are:

Tablet core: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone K30, colloidal anhydrous silica and sodium laurilsulfate.

Tablet coating: Hypromellose 2910, lactose monohydrate, macrogol 3350, titanium dioxide and triacetin. Iron oxides are also included in the film coating mixes as follows:

- Iron oxide red (E172) in 3 mg, 4 mg, 7 mg, 8 mg, 9 mg, and 10 mg film-coated tablets;
- Black iron oxide (E172) in 4 mg, 5 mg, 8 mg, and 9 mg film-coated tablets;
- Iron oxide yellow (E172) in 3 mg, 5 mg, 7 mg, 9 mg, 10 mg, and 20 mg film-coated tablets.

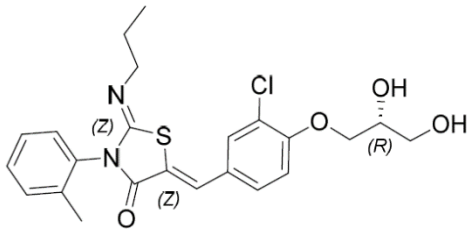
The product is available in Alu/Alu blisters.

2.2.2. Active Substance

General information

The chemical name of ponesimod is (2*Z*,5*Z*)-5-[3-chloro-4-[(2*R*)-2,3-dihydroxypropoxy]benzylidene]-3-(2-methylphenyl)-2-(propylimino)-1,3-thiazolidin-4-one corresponding to the molecular formula $C_{23}H_{25}ClN_2O_4S$. It has a relative molecular mass of 460.97 g/mol and the following structure:

Figure 1: Active substance structure



The chemical structure of ponesimod is inferred from the route of synthesis and further elucidated by a combination of elemental analysis, infrared spectroscopy, ultraviolet spectroscopy, ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry with single crystal x-ray structure analysis to confirm absolute configuration of the single (*R*)-stereocentre. The solid-state properties of the active substance were measured by Raman spectroscopy, differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), x-ray powder diffraction (XRPD), and gravimetric vapour sorption (GVS).

The active substance is a white to light yellow non-hygroscopic crystalline powder. Different polymorphic forms were identified throughout development. The manufacturing process routinely delivers the commercial polymorph.

Ponesimod exhibits stereoisomerism due to the presence of one chiral centre.

Manufacture, characterisation and process controls

Ponesimod is synthesised in three main steps using well defined starting materials with acceptable specifications.

The process is sufficiently described. A DoE study indicated ranges for each of the input materials within which the levels of critical impurities are kept sufficiently low and the yield is acceptable. These ranges are defined as a design space which is deemed acceptable. The critical steps and in-process controls are adequately defined and deemed suitable for controlling the manufacturing process. The specifications for the starting materials and intermediates are acceptable.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. The CHMP raised a major objection due to a lack of information on the potential presence of mutagenic impurities. In response, the applicant provided a detailed report covering actual and potential mutagenic impurities, mutagenicity screening, as well as fate and purge studies and calculations. The CHMP concluded that the information was acceptable. Potential and actual impurities were well discussed with regards to their origin and characterised.

The development of the ponesimod route of synthesis has been discussed, with process iterations and optimisations from lab to production scale. Changes introduced have been presented in sufficient detail and have been justified.

The active substance primary packaging complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification set according to ICH Q6A includes tests for appearance (visual examination), identity (IR), residue on ignition (Ph. Eur.), residual solvents (GC), impurities (HPLC), assay (HPLC) and particle size distribution (laser light diffraction).

Limits for impurities are set according to ICH Q3A and are considered appropriate. The manufacturing process routinely delivers the desired polymorphic form.

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 from three production scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 3 production scale batches of active substance from the proposed manufacturer stored in packaging representative of the intended commercial package for up to 48 months under long term conditions (30ºC / 65% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. Samples were tested for appearance, assay, chromatographic purity and particle size distribution. The analytical methods used were the same as for release and are stability indicating. In addition, colour and clarity of a solution, polymorphism, water content, enantiomeric purity and microbial purity were tested. The methods used are described in the dossier.

No significant trends were observed for any measured parameters. All tested parameters remained within the specifications. The results from the additionally tested parameters justify the omission of these tests from the specification.

Photostability testing following the ICH guideline Q1B was performed on one batch. Ponesimod is photosensitive and is stored protected from light.

Forced degradation studies were carried out on one batch subjected to heat and moisture in the solid state, light in the solid state, acid and basic conditions in solution, and an oxidizing agent in solution. Ponesimod in the solid state is stable when exposed to high temperature and humidity but is sensitive to light. Degradation occurs in solution at basic or acidic pH and when exposed to an oxidant or radical initiator.

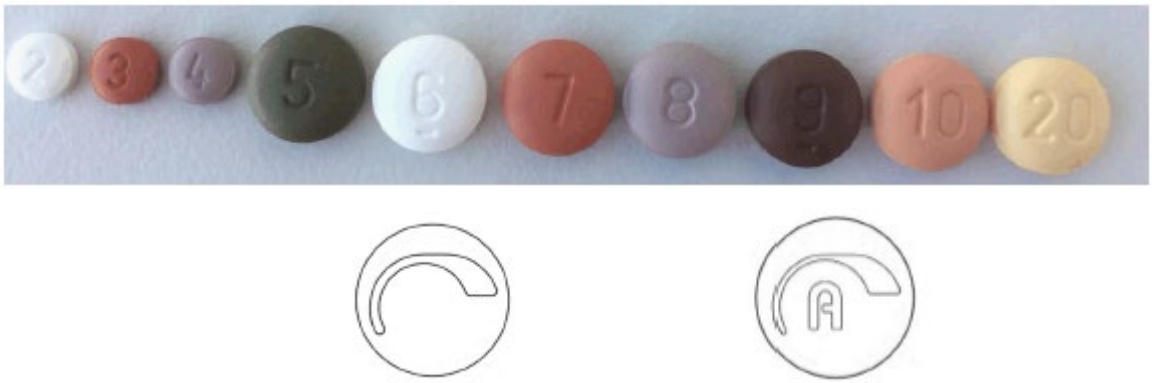
The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container protected from light.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is presented as immediate-release film-coated tablets containing 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg or 20 mg of ponesimod as active substance. The different strengths are distinguished by size, colour and debossing as indicated in Figure 2. On the back face, all tablets are debossed with an arch. Additionally, the larger tablets (5-20 mg) are debossed with an "A" as indicated at the bottom of the figure.

Figure 2: Appearance of finished product



The aim of development was to produce an immediate release dosage containing multiple strengths of the active substance. Accordingly, a quality target product profile (QTPP) was developed and is summarised in along with the related critical quality attributes (CQAs) in **Table 1**.

Table 1: Ponvory QTPP

Drug Product Attribute	QTPP Aspect	Drug Product CQA
Dosage Form	Film-coated tablet	Appearance
Route of Administration	Oral	Appearance
Dosage Strength	2, 3, 4, 5, 6, 7, 8, 9, 10, and 20 mg of ponesimod	Appearance, identification, assay, uniformity of dosage units
Purity	Sufficiently low level of impurities/degradation	Chromatographic Purity

	products, complying with the ICH requirements	
Drug Release Profile	Immediate release	Dissolution
Microbiological Purity	Sufficiently low level of microbial burden, complying with the ICH requirements	Microbiological Purity
Container Closure System	Blisters or bottles	Chromatographic purity, dissolution
Stability	Minimum 36 months shelf-life	Appearance, assay, chromatographic purity, dissolution, microbiological purity

The excipients chosen are typical for this type of dosage form and compatibility with the active substance was shown in studies on binary mixtures. 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 and in paragraph 2.2.1 of this report.

In early clinical studies, a hard capsule formulation was used. The formulation was changed to a film-coated tablet containing the proposed commercial polymorphic form of the active substance for later clinical studies. Bioequivalence between the formulations was demonstrated clinically. Changes to colour and debossing were made after phase 3 trials and are not expected to impact bioavailability.

The applicant described the development of the proposed dissolution method. The CHMP raised a major objection to the originally proposed dissolution method as the dissolution rate was rapid and the use of a surfactant had not been justified. In response, the applicant submitted a re-developed method. Discriminatory power was investigated in relation to changes in relevant manufacturing parameters and material attributes. The applicant committed to further investigate discriminatory power in relation to more extreme changes in manufacturing parameters and the functional properties of excipients and report the results back to the agency. The revised dissolution method is considered to acceptable, as is the specification limit.

The development of the manufacturing process was described in detail. For each unit operation and step, the potential impact on the CQAs was assessed and investigated experimentally. Ranges for further investigation were thus identified. Proven acceptable ranges (PARs) have been defined for certain process parameters. In general, the formulation development work is adequately explained.

The primary packaging is an Alu/Alu blister with desiccant consisting of a laminated Alu cold form film with integrated desiccant and a laminated Alu push-through lidding film. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of 11 main steps: dry blending; preparation of granulation solution; wet granulation; drying; screening; blending; lubrication; compression; preparation of film-coating suspension; film-coating; packaging. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated using a bracketing approach given the high number of strengths and considering the similarity between the dose strengths. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended

quality in a reproducible manner. Critical steps have been defined, along with intermediates. The hold time for the bulk tablets has been justified with stability data. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including appearance (visual examination), identification (HPLC, UV), uniformity of dosage units (Ph. Eur.), assay (HPLC), degradation products (HPLC), dissolution and microbial purity (Ph. Eur.).

The potential presence of elemental impurities in the finished product was assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. It was concluded that there is a negligible risk of elemental impurities based on the process, raw materials, and manufacturing equipment. This was confirmed with analysis data from 4 batches of active substance and 3 batches of finished product using a validated ICP-MS, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that no elemental impurity controls are needed.

A risk evaluation concerning the potential presence of nitrosamine impurities in the finished product was submitted in response to a major objection from CHMP. The assessment considered 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). There are no confirmed sources of nitrosating agent. Based on the information provided it is accepted that no risk was identified of the possible presence of nitrosamine impurities in the active substance or the related finished product and no additional control measures are deemed necessary.

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 for the 20 batches produced during process validation confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the release specifications, through traditional final product release testing.

Stability of the product

Stability data from the 18 batches of finished product manufactured at 50% production scale in the validation campaign and using the same bracketing approach, stored for up to 36 months under long term conditions (25ºC / 60% RH), 36 months under intermediate conditions (30ºC / 75% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of finished product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

All relevant quality attributes were monitored: appearance, assay, degradants, dissolution and microbial purity were investigated. In addition, water content was measured. No significant change was observed for any strength after 6 months under accelerated conditions.

Under long term and intermediate conditions, no significant changes in the physical, chemical and pharmaceutical characteristics are to any of the measured parameters were observed, except for a decrease in water content over time. This trend was attributed to the presence of the desiccant.

In addition, one batch of each strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Ponvory tablets are photostable.

Based on available stability data, the proposed shelf-life of 36 months without special storage conditions as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.2.4. 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, the applicant was able to resolve the three major objections raised by CHMP by providing additional data as follows: the evaluation of potentially genotoxic impurities was adequately explained; a risk assessment for the potential presence of nitrosamine impurities was submitted, indicating that there isn't a risk of nitrosamines contamination; the dissolution method has been replaced and the new method is seen as sufficiently discriminatory. Further development work and investigation of discriminatory power will be conducted post-approval (see recommendation). The design space covering the quantities of input materials in steps 2-3 of the active substance manufacturing process has been justified.

2.2.5. 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. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- The applicant should further investigate the discriminatory power of the dissolution method in relation to more extreme changes in manufacturing parameters and the functional properties of excipients and report the results back to the agency.

2.3. Non-clinical aspects

2.3.1. Introduction

2.3.2. Pharmacology

Primary pharmacodynamic studies

The primary PD of ACT-128800 (ponesimod) have been evaluated in a comprehensive panel of *in vitro* and *in vivo* studies.

In vitro

The potency and agonist activity of ACT-128800 were determined in a guanosine triphosphate (GTP) γS-binding assay, a cyclin adenosine monophosphate (cAMP) accumulation assay and a ^{33}P-S1P radioligand-displacement assay. ACT-128800 proved more effective than the natural ligand S1P on $S1P_1$, whereas ACT-128800 was not able to activate sphingosine 1-phosphate receptor 2 ($S1P_2$) at concentrations of up to 10 µM. In addition, ACT-128800 was less potent in activation of the sphingosine 1-phosphate receptor 3 ($S1P_3$) (associated with bradycardia) than S1P but was able to fully activate $S1P_3$ at higher doses. A 5-fold reduced potency on rat $S1P_3$ receptor was observed as compared to the human counterpart. Also, pFTY720, a non-selective S1P receptor modulator, was not able to fully activate rat $S1P_3$. In addition, was ACT-128800 not able to fully activate the sphingosine 1-phosphate receptor 4 ($S1P_4$) receptor as compared to S1P and pFTY720 and it had a higher potency but lower efficacy in activating sphingosine 1-phosphate receptor 5 ($S1P_5$) than S1P. No agonist activity of ACT-128800 was detected in activating lysophosphatidic acid receptors (LPA), LPA1 LPA2 and LPA3 receptors.

Various metabolites of ACT-128800 have been identified in human plasma of which M12 (ACT-204426) and M13 (ACT-338375) were determined as the most abundant ones. Therefore, the potency, as well as the agonist activities of these major metabolites on the five human S1P receptors, was comparatively determined with the natural ligand S1P in vitro. GTPγS assays in membrane preparations from Chinese hamster ovary (CHO) cells expressing recombinant S1P receptors revealed that M12 and M13 are 10 and 20 times, respectively, less potent than S1P on the $S1P_1$ receptor. No or negligible potency of M12 and M13 was observed on $S1P_2$, $S1P_3$, $S1P_4$ and $S1P_5$. These results were essentially confirmed by a resonant waveguide grating (RWG)-based assay.

The lymphopenic effect of ACT-128800 is assumed to be exerted by $S1P_1$ receptor agonists via transient receptor desensitisation by internalisation. The effect of the natural ligand S1P, as well as ACT-128800 and pFTY720 on receptor internalisation, was evaluated in a cell-based assay employing recombinant CHO-K1 cells. ACT-128800 and pFTY720 triggered sustained receptor internalisation with similar efficacy and potency at concentrations > 100 nM. In contrast, S1P caused transient receptor internalisation at concentrations < 100 nM. At higher concentrations, S1P induced a persistent decrease in receptor expression. This difference between synthetic and natural $S1P_1$ ligands is explained by the applicant by differences in the dissociation of the ligands from the receptor, i.e. that the natural ligand allows rapid resurfacing of the receptor by rapid dissociation which appears to be not the case with synthetic ligands.

S1P-induced activation of $S1P_1$ and $S1P_3$ receptors are known to mediate extracellular signal-regulated kinase 1/2 (Erk1/2) and Ras-related C3 botulinum toxin substrate 1 (Rac1) signalling, which, in turn, is critical for cell survival and proliferation. A difference in the effect mediated by natural or synthetic ligands of the $S1P_1$, i.e. transient and sustained receptor desensitisation has already been observed. An additional cell-based study (#B-17.009) revealed that FTY720 appears to be the most potent inducer of

Erk1/2 phosphorylation, whereas ACT-128800 was about 50-fold less potent and the natural ligand S1P was 200-fold less potent when cells were stimulated for 10 minutes with the respective compound. When cells were continuously exposed to ACT-128800 Erk1/2 signalling could not be elicited via S1P or ACT-135364 (a close ponesimod analogue) suggesting that chronic ACT-128800 exposure makes cells refractive for further $S1P_1$ stimulation. This was confirmed by detection of lower $S1P_1$ protein levels in cells exposed to ACT-128800 over three days. This effect was observed irrespective of removal of ACT-128800 after three days. When cells were allowed to recover for 24 hours after 24 hours incubation with ACT-128800 a full recovery of the $S1P_1$ expression was observed.

Taken together, these findings demonstrate that chronic ACT-128800 exposure makes cells unresponsive to further stimulation by receptor internalisation and does not lead to permanent signalling.

In vivo

Single oral administration of ACT-128800 (3, 10, 30, 100 mg/kg; n=6/dose group; Study #B-05.053) reduced lymphocyte levels in rats in a time- and dose-dependent manner. The maximal reduction in lymphocyte levels was achieved at a plasma concentration of 70 ng/ml in rats and occurred at 3 and 6 hours at the lowest dose level. The duration of the lymphocyte reducing effect very well correlated with the dose administered, i.e. the higher the dose, the longer lasted the effect.

Single oral administration of 5 mg/kg ACT-128800 to conscious beagle dogs (Study #B-05.126) resulted in a reduction in lymphocyte counts from baseline ranging from 39–58% after 4 hours and 52–70% after 24 hours. Recovery of lymphocyte counts appeared to depend on the administered dose and, as a consequence, on plasma levels of ACT-128800.

In CD-1 mice repeated oral administration of ACT-128800 for 5 days (Study# B-17.008) reduced circulating lymphocyte counts with a peak effect at 2 and 6 hours after the last oral administration to a level of 1000-1400 lymphocytes/µL (mean values of n = 4-5) at all doses tested (50, 150, and 400 mg/kg). In the vehicle group mean values at d0 (baseline), 2h, 6h, and 24h after last administration were 7.2, 4.2, 5.0 and 5.0 x 103 cells/µl. Moreover, it was noted that the effect on lymphocyte counts exerted by ACT-128800 was not dependent on dose and plasma-levels, respectively, as group mean values after the last administration of 10, 150 and 400 mg/kg were 1.0, 1.4 and 1.2 x 103 cells/µl after 2h and 1.4, 1.0 and 1.1 x 103 cells/µl after 6h. This suggests that the maximal pharmacological effect was already achieved at the lowest dose of 10 mg/kg/day. After recovery at 24h after the last administration of 10, 150, and 400 mg/kg mean lymphocyte counts were 6.9, 6.1 and 4.2 x 103 cells/µl, respectively. A dose-effect on the recovery of lymphocyte counts cannot be ruled out from these data.

The effect of ACT-128800 on the reduction of lymphocyte subsets was investigated after repeated administration of 3, 10 and 30 mg/kg over 7 days in rats. Lymphocyte subsets especially prone to $S1P_1$-mediated reduction were naïve CD4+ and CD8+ cells as well as γδ T-cells and Natural Killer T (NKT). Natural Killer (NK) cells and monocytes were hardly reduced upon ACT-128800 treatment. Only slight variation with regard recovery was observed between the investigated lymphocyte subsets, i.e. αβ T-cells, γδ T-cells, B cells, NK cells and NKT cells, as well as monocytes. NKT cells, however, appeared to return to baseline more rapidly. FTY720 reduced all lymphocyte subsets to a similar extent as ACT-128800. However, in contrast to ACT-128800, lymphocyte reduction and, thus, the return to baseline was prolonged in FTY720 treated animals.

The therapeutic efficacy of ACT-128800 was investigated in a murine Experimental Autoimmune Encephalomyelitis (EAE) model (Study #B-08.460), in which mice were immunised with a peptide derived from myelin oligodendrocyte glycoprotein (MOG) together with strong bacterial adjuvants and pertussis vaccine to generate a MS-like condition. Treatment with 30 mg/kg twice a day (BID) ACT-128800 for 23 days starting on day 1 after induction of the disease resulted in the suppression of clinical

signs of the disease also throughout the 7-day treatment-free follow up period. Less effectivity was observed when treatment was started with 6 mg/kg BID only 6 days after immunisation. In an additional subset of animals, treatment with 30 mg/kg BID was only started on day 15 after immunisation when animals already displayed clinical signs of the disease. In the 31 day-experiment, mice continuously treated with ponesimod 30 mg/kg BID from day 1–31 showed 90% survival, and mice in which the treatment with ponesimod was started only on Day 15, showed survival rate of 60% on day 31, however, clear clinical signs of paralysis were apparent in both groups as shown by decrease in clinical score from 4 in untreated mice to 3 in ponesimod treated mice. The histology on brain and spinal cord tissues clearly demonstrate decreased mononuclear cell infiltrate in ponesimod 30 mg/kg bid treated mice. The applicant was expected to discuss the development of paralysis in ponesimod bid treated EAE mice in the absence of CNS inflammation. The applicant explained that the representative CNS histology data shown in the report B-08-460 were derived from a 30-day preventive experiment (Exp A and Exp B) where ponesimod was administered at 30 mg/kg bid orally, starting on Day 1 after immunisation with MOG peptide (prevention study). In a 31-day treatment study, mice treated with ponesimod from Days 1–31 showed 90% survival, whereas survival rate was 60% in mice treated after clear onset of EAE symptoms, starting from day 15. Clinical severity was clearly worse in the 31-day (treatment) experiment, in comparison to the preventive 30-day experiment. Since histology analysis of CNS pathology from a 31-day treatment experiment was not performed, the influx of the immune cells in the CNS cannot be established as a cause of the paralysis. Nevertheless, the results from the EAE mouse model indicate that the administration of ponesimod slows down the disease progression and increases survival rate in the mice that received ponesimod comparing to the vehicle-treated animals.

ACT-128800 treatment was capable of slowing disease progression and increasing survival in these mice as compared to vehicle-treatment but was not as effective as treatment starting before the development of clinical signs. Histological analysis revealed protection against axonal damage or loss. Anti-MOG antibodies were still present after ACT-128800 treatment also indicating other pathomechanisms apart from antibody-mediated disease involved in EAE. Antigen-specific T-cells were detectable in spleens of animals of all treatment or vehicle groups. However, the proliferation of MOG-antigen-specific T-cells was diminished to a certain extent ex vivo when incubated with ACT-128800. The applicant concluded that, because ACT-128800 did not prevent the formation of MOG peptide-specific T cell clones, a reduction in the trafficking of MOG-reactive T-cells to the CNS might occur.

The hypothesis that ACT-128800 regulates the circulation of T-lymphocyte trafficking between blood, lymphatic system and non-lymphoid tissues was evaluated in a delayed-type hypersensitivity model in mice. Skin inflammation was induced by topical administration of dinitrofluorobenzene (DNFB) and ACT-128800 was administered orally (30 mg/kg) before (19 and 3 hours) sensitisation and for further 8 days thereafter (1g/kg food). Inflammatory parameters (ear oedema, recruitment of neutrophils to the skin and protein extravasation in the ear skin) were reduced by 60 to 91% in the ACT-128800 treated group as compared to vehicle.

The efficacy of ACT-128800 was evaluated in an additional T-cell mediated inflammation model in rats, i.e. adjuvant-induced arthritis (AIA). AIA was induced by intradermal injection of 0.1 mL Complete Freund's adjuvant (CFA; 6 mg heat-inactivated Mycobacterium tuberculosis H37 RA in 1 mL liquid paraffin Freund's adjuvant incomplete). Mice were treated orally with ACT-128800 starting from day 0 of disease induction through 16 days with 1 or 6 mg/kg BID or 0.3 mg/kg FTY720 once a day (QD). A dose-dependent pharmacological effect could be observed whereby the 6 mg/kg dose efficiently delayed onset and reduced the development of clinical signs of the disease. A clear amelioration of the symptoms was achieved with 1 mg/kg as compared to the vehicle group. Correspondingly, peripheral lymphocyte counts were reduced in a dose-dependent manner.

In a second experimental setting, animals were treated with 30 mg/kg ACT-128800 and inoculated with CFA three hours thereafter. A second oral dose was given 9h after the first dose. In addition, feed supplemented with ACT-128800 (1 g/kg) was administered to animals for an additional 18 days. For the first week of the experiment, no difference in inflammation marker levels was observed between treatment and vehicle groups. According to the applicant, this observation can be explained by an acute inflammatory reaction at the injection site. Starting from day 14, a clear reduction of inflammation markers (c-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) were observed in ACT-128800 treated mice as compared to the vehicle group. In addition, significantly lower levels of pro-inflammatory cytokines (human growth-regulated oncogene/ Keratinocyte chemoattractant [GRO/KC], Interleukin [IL]-1ß, IL-6, IL-12(P70), IL-17, IL-18, monocyte chemoattractant protein-1 [MCP-1], macrophage inflammatory protein-1 alpha [MIP-1α], regulated upon activation, normal T cell expressed and presumably secreted [RANTES]), as well as the bone erosion marker receptor activator of nuclear factor kappa-B ligand (RANKL), were detected in ACT-128800-treated animals in comparison to animals administered with vehicle.

The PD effect of ACT-128800 was further evaluated in MRL/lpr mice that spontaneously develop a systemic lupus erythematosus (SLE)-like disease. SLE is a T- and B-cell driven disorder. MRL/lpr mice develop serum autoantibodies at 6 weeks of age and lymphadenopathy at 12 weeks (Liu et al., 2006). The disease is mediated by the emergence of an unusual population of B220+CD4negCD8neg T cells (double negative). Mice develop progressive renal disease, including heavy proteinuria by 16 weeks of age and 50% die at 20 weeks. Other morbidities observed include progressive lymphadenopathy/splenomegaly, hypergammaglobulinemia, autoantibody production (e.g. anti-DNA), immunocomplex formation and multiple organ alteration, e.g. vasculitis, arthritis and fatal glomerulonephritis. Generally, MRL/lpr mice do not survive longer than 28 weeks.

Mice were treated with ACT-128800 starting from 12 days of age for 12 weeks. Treatment was initiated with oral gavage of 30 mg/kg for one day and maintained by food mixed with ACT-128800 (1 g/kg food). Clinical scores were determined for skin lesions, arthritis, lymphadenopathy and body weight. In addition, analysis for proteinuria and albuminuria was performed. Plasma was analysed for cytokines, immunoglobulin isotypes, anti-DNA antibodies and B cell-activating factor (BAFF). Splenocytes and lymph node cells were analysed by flow cytometry to determine B- and T-cell subsets. Histopathological analysis of kidneys was performed in order to detect abnormalities.

Mice did not develop notable signs of arthritis and skin lesions in this study. The increase of the albumin to creatinine ratio was delayed and suppressed in ACT-128800 treated animals as compared to the vehicle group. Nephropathy and glomerulonephritis appeared less severe in animals that received ACT-128800. Lymphoproliferation in secondary lymphoid organs, i.e. lymph nodes and spleen, was reduced by ACT-128800 and all investigated lymphocyte subsets were decreased in blood but not in lymph nodes. No effect on auto-antibodies was exerted by ACT-128800, but IgA and BAFF were found to be decreased. Except for a small decrease of plasma Interferon gamma-inducible protein (IP-10) no effect on cytokines was observed. Survival was not significantly prolonged by ACT-128800 as compared to the vehicle group.

Thus, ACT-128800 showed a beneficial effect on the development of the SLE-like disease in MRL/lpr mice, that was in particular apparent in the prevention of kidney disease, lymphadenopathy and circulating lymphocytes.

Secondary pharmacodynamic studies

Interaction of ACT-128800 with a comprehensive panel of 107 protein-coupled receptors, enzymes, ion channels and transporter proteins was evaluated by radioligand-binding or activity assays (Study #B-05.112). Weak effects were only observed with the endothelin receptor type A (ETA), monoamine oxidase

(MAO)-B, and protein serine/threonine kinase (Ca2+/calmodulin-dependent II) at a relatively high concentration of 10 µM as compared to a half maximal effective concentration (EC_{50}) in the GTPγS assay. The effects are therefore considered not relevant for therapeutic concentrations of ACT-128800.

The effect of ACT-128800 on the course of and the immune response to an infection was tested in mice infected with L. monocytogenes (Study #B-17.048). Mice were infected with 1 x 103 colony-forming unit (CFU)/animal at day 0. Treatment with ACT-128800 started on day -1 with an oral dose of 100 mg/kg BID and was continued until day 9 post-infection. On day 3 after infection relative proportions of CD4+, CD8+ and B220+ peripheral blood lymphocyte subsets were comparable in ACT-128800- and vehicle-treated animals. CFUs isolated on days 2, 6 and 10 from spleens, kidneys, livers and lungs of infected animals treated with ACT-128800 and vehicle revealed a similar course of infection in animals with or without treatment with ACT-128800.

Essentially, the risk of a difficult progression of bacterial infections under ACT-128800 treatment is considered low. This is in line with clinical observations made with a nonselective SP1 modulator.

Safety pharmacology programme

For the elucidation of potential effects on the cardiovascular system, the capability of ACT-128800 and its major metabolite M13 to cause QT-prolongations was investigated in *in vitro* human ether-à-go-go related gene (hERG)-channel assays (Studies #T-04.092 and B-10.608). Both compounds were found to be weak inhibitors of the hERG-mediated potassium current with an 20% inhibitory concentration (IC_{20}) of 3 µM or 5-8 µM, respectively. ACT-128800 and M13 were tested independently in two separate studies that employed different cell lines, stimulation protocols and positive controls; nevertheless, no concerns with regard to potential QT-prolongations exist.

A dose-related increase in the HR (heart rate), which regressed after repeated administration was observed in patients treated with ACT-128800. As no such findings were made in rat and dog safety pharmacology studies, a possible direct (as opposed to indirect through neural control of the HR) influence of ACT-128800 on the firing rate of isolated sinus node preparations of different species (male and female Wistar rats, male guinea pigs and female New Zealand white rabbits) was investigated (Study #B-08.043). No increased in the firing rate was observed at concentrations of up to 10 µM largely precluding a direct influence of ACT-128800 on the HR.

In terms of investigating vascular effects of ACT-128800 a set of *in vitro* experiments was performed with different types of arteries derived from dogs, rats and human patients. ACT-128800 mediated low contraction in rat basilar arteries when the endothelium was intact and a more pronounced contraction when the endothelium had been removed (Study #B-05.081). Similar observations were made with S1P. Pre-treatment with an $S1P_3$ antagonist inhibited S1P-mediated contraction. In contrast, ACT-128800 had a relaxing effect on pre-contracted rat aorta. These observations were explained by the applicant by the high ratio of $S1P_3$ to $S1P_1$ in rat arteries, whereas the ratio is the other way around in the rat aorta.

An additional *ex vivo* experiment was conducted to investigate species differences in the contractile properties of ACT-128800 on arteries (Study #B-08.456). Mesenteric arteries from rats and dogs differently reacted to ACT-128800 exposure: whereas no contraction was observed in rat mesenteric arteries at concentrations of up to 1 µM, dog mesenteric arteries already contracted at an exposure to a 100 nM ACT-128800 solution. From these results, a differential effect of ACT-128800 on the blood pressure (BP) in rats and dogs, as observed in *in vivo* studies, would be conceivable. In contrast to ACT-128800, mesenteric arteries from both rats and dogs, were highly responsive to pFTY720.

In order to investigate the sensitivity of dog coronary arteries to ACT-128800-mediated contraction, a comparative experiment with rat coronary arteries was conducted (Study #B-08.069). Selective blocking

of $S1P_3$ revealed that contraction in dog arteries is mediated by $S1P_3$ receptor binding. Activation of $S1P_1$, in contrast, counteracted the contraction of dog arteries. Moreover, it was found that injury of the endothelium augments the contractile effect on canine arteries. On the molecular level, it was revealed that the species difference with regard to ACT-128800 mediated contractility is established by a different expression pattern of $S1P_1$ and $S1P_3$. Thus, dog arteries express predominantly $S1P_3$ messenger ribonucleic acid (mRNA), whereas rat arteries highly express $S1P_1$ mRNA. In in vitro PD studies ACT-128800 was found to have a 5-fold reduced potency on rat $S1P_3$ receptor as compared to the human counterpart. Nevertheless, the rat is considered a relevant species for the evaluation of the safety of ACT-128800. This is based on the one hand on the complexity of the actual physiological response of $S1P_3$ signalling as compared to *in vitro* studies and on the other hand on the totality of data that have been generated *in vivo* and *ex vivo* in various species.

Arteries isolated from rats treated with ACT-128800 or fingolimod for four weeks did not show any differences in response to various vasoconstrictors as compared to vehicle-treated animals, indicating no persistent change induced by ACT-128800.

Finally, arterial rings (left anterior descending, right coronary artery and internal mammary artery) from six patients were investigated with regard to responsiveness to ACT-128800 induced contraction (Study #B-08.457). Human arterial rings responded only minimally to a concentration of 100 nM ACT-128800, which corresponds to the available amount of free compound *in vivo*. Supra-therapeutic concentrations of 1 µM ACT-128800 triggered a contraction in human arteries. The expression profile of $S1P_1$ and $S1P_3$ mRNA was similar in both coronary and internal mammary arteries. Thus, from the *ex vivo* data provided for human arteries, it can be deduced that ACT-128800 does not have a vasoconstrictive effect on human arteries at therapeutic concentrations. However, it has to be noted that the endothelium appeared not to be functional in all of the human preparations as they were derived from surgery of patients with coronary disease and there was a longer time lag between excision and ex vivo evaluation negatively affecting the function of the epithelium.

The *in vivo* effect of ACT-128800 on the cardiovascular system was investigated in a series of studies:

Single oral administration of doses of up to 600 mg/kg (corresponds to a plasma exposure of 3.7 µg/mL) did not result in changes of the HR or of mean arterial BP in comparison to vehicle when observed for 24 hours after treatment (Study #B-08.461).

Repeated daily administration of 30 mg/kg/day ACT-128800 or 1 mg/kg/day FTY720 lead to a late-onset or immediate increase in mean arterial BP but did not affect HR (Study #B-16.016). The low doses of 10 mg/kg/day ACT-128800 or 0.3 mg/kg/day FTY720 did not have any effect on BP. Lung weights dose-dependently increased under ACT-128800 and FTY720 treatment for 20% - 65% and 24% - 47%, respectively. Neither compound had an influence on the heart weights. Lymphocyte counts were similarly reduced in both ACT-128800 and FTY720 treated animals.

Two studies in spontaneously hypertensive rats revealed that a single dose of 100 mg/kg (corresponding to a plasma concentration of 1000 ng/ml) did not have an effect on the BP or HR when administered in the morning (Study #B-05.054). Upon evening administration, thus, before the activity phase of the animals, still no effect on BP was observed but the normal increase of the HR at that time was less pronounced with 100 mg/kg (Study #B-07.401). FTY720, on the other hand, increased the BP and decreased the HR of normotensive and spontaneous hypertensive animals starting from doses of 3 mg/kg.

A reduction of HR and, occasionally, AV block type II, Wenckebach has been reported in patients treated with FTY720. ACT-128800 was also found to affect HR and rhythm in healthy human subjects. These effects were largely limited to day 1 of treatment. For further investigation of this observation, cardiovascular parameters in response to ACT-128800 treatment were investigated in conscious

telemetered Guinea pigs (Study #B- 08.040). A single administration of 0.1 mg/kg did not have any effect. However, 0.3 mg/kg induced AV Block type III in one animal and 3 mg/kg in all animals. A transient decrease in BP was observed at doses starting from 1 mg/kg. When repeated doses of 1 or 3 mg/kg were administered, desensitisation was observed so that the second administered dose did elicit considerably weaker effects than the first dose. Effects evoked by the first dose were AV block II, Mobitz II and AV block type III. It was observed that the effects of the second dose were largely dependent on the plasma concentration at the time point of the second administration, i.e. it was more pronounced when plasma concentrations had already declined again. It was further discovered that a gradual increase of the dose, starting with very low doses of 0.1 mg/kg could largely prevent the occurrence of AV blocks.

A dose-dependent effect of ACT-128800 on cardiac parameters was also observed in anaesthetised guinea pigs that were administered via infusion (Study #B-08.041). The effects, i.e. AV blocks type I, II and III, were apparent, starting from doses of 0.03 mg/kg administered over 20 minutes and lasted for 20-35 minutes. ACT-128800 induced cardiac effect could be reversed by β-adrenoceptor agonists but not by atropine, a muscarinic receptor antagonist.

Guinea pigs appear to be more sensitive to ACT-128800 as compared to rats as effects on the BP, and HR were already observed at single-doses of 1 mg/kg whereas in rats no effects were observed after single doses of up to 600 mg/kg. Moreover, upon repeated administration of ACT-128800 rats and dogs developed an increased BP, whereas the BP decreased in guinea pigs in response to ACT-128800. Also, no effect on the HR was observed at any dose in rats and dogs. However, integrating the effects observed in humans, rats and guinea pigs renders guinea pigs a relevant species for the investigation of cardiovascular effects of ACT-128800 despite higher sensitivity.

As an additional species for the investigation of potential effects on cardiac function, telemetered conscious beagle dogs were administered with single doses of 0.6, 1.4 and 4 mg/kg ACT-128800 by infusion over 30 minutes (good laboratory practice [GLP]; Study #T-05.047). No effects on electrocardiogram (ECG), HR or BP were observed so that the no observed effect level (NOEL) on cardiovascular parameters was determined at 4 mg/kg intravenous administration. Oral administration of 10, 30 or 100 mg/kg resulted in a transient increase in BP in some animals starting at a dose of 30 mg/kg. HR, electrocardiographic parameters, respiratory parameters (respiratory rate, tidal volume and minute volume) and locomotor activity were not affected at any dose administered. The oral NOEL for ACT-128800 was therefore set at 10 mg/kg.

Daily administration of 40 mg/kg ACT-128800 for four weeks to telemetered Beagle dogs lead to a significant daily increase in systolic (SPB) and diastolic blood pressure (DBP) mainly up to 2 hours after administration (GLP; Study #T-07.185). The increase of the BP correlated with plasma levels of ACT-128800 and was most pronounced after the first treatment. This finding is in line with the desensitisation to ACT-128800-related effects observed in guinea pigs. HR and the general health status, as well as body weight (BW) and food consumption, were not influenced by ACT-128800 treatment. After the *in vivo* observation period, large coronary arteries, their smaller branches, and the interventricular septum were subjected to $S1P_1$ and $S1P_3$ gene expression analysis. No statistically significant difference was observed in regard to $S1P_1$ expression in all tissues investigated. $S1P_3$, in contrast, was higher expressed in large coronary arteries and the interventricular septum as compared to the arterial branches. No influence of ACT-128800 on the receptor expression pattern was observed.

Finally, the effects of ACT-128800 on both cardiac and peripheral vascular areas were investigated in an open-chest model of anaesthetised dogs (GLP; Study #T-07.245). ACT-128800 was administered at doses of 0.6, 1.4, 4 and 8 mg/kg/30 min at 4 increasing rates of infusion of 0.12, 0.28, 0.8 and 1.6 mL/kg over 30-minute periods. A dose-dependent hypertensive effect was observed starting from doses

of 1.4 mg/kg. The observed effect was found to be related to a vasoconstrictive action of ACT-128800 on peripheral vascular areas.

In vivo assessment of effects mediated on the respiratory system of rats by whole-body plethysmography revealed that ACT-128800 statistically significantly increased Penh values after a single dose of 100 mg/kg 3 and 6 hours after administration (GLP, Study #B-05.090) and was only observed when the plasma concentration of ACT-128800 was approx. 3800 ng/mL or higher. In contrast, FTY720 lead to a statistically significant increase of Penh at a dose of 10 mg/kg at 3, 6 and 24 hours after treatment. Analysis of individual respiratory parameters revealed that the increase in Penh is most likely caused by a decrease in the relaxation time.

Similarly, in a GLP-compliant 4-week oral administration (10 or 100 mg/kg/day) study including a two-week recovery period (Study #T-06.047), the main effects observed were a dose-dependent statistically significant increase in peak expiratory flow and enhanced Penh after the first administration. These effects were still noted after two weeks of consecutive treatment. However, the effect was higher in the 10 mg/kg dose group. This increase in Penh was not considered as a signal for bronchoconstriction but rather as resulting from a more than proportional increase in peak expiratory flow (PEF) compared to peak inspiratory flow (PIF). After four weeks of treatment and the recovery period, no more effects on respiratory parameters were noted. Histopathologic examination after the recovery period revealed alveolar histiocytosis in both dose groups and alveolar hyalinosis in one out of eight animals. Moreover, dose-dependent perivascular lymphoid cell infiltration was noted in all groups, including controls. No other treatment-related events were detected.

Vascular permeability in response to single or repeated oral dosing for 14 days of up to 100 mg/kg ACT-128800 was assessed in rats (Study #B-09.392). Evans blue was used as a marker for vascular permeability. For single dosing, an increase in permeability was observed starting from doses of 1 mg/kg with a maximum effect 3-7h after administration and full reversibility within 24 hours. Maximal permeability was noted at 4 mg/kg with no further increase of the effect with increased doses. No increase in lung permeability was observed upon chronic treatment with 10 or 100 mg/kg/day. However, a time-dependent decrease in lung permeability could be detected in the second week of treatment as compared to the first administration. In contrast, the weight of the lungs increased in a dose-dependent manner and persisted throughout the treatment period. Thus, the lung seems to adapt to chronic administration of ACT-128800.

In order to investigate the mechanism behind the alveolar histiocytosis, increase in lung weights and hyperplasia a study with single and multiple (for seven days) administration of 100 mg/kg ACT-128800 was conducted in rats (Study #B-09.073). In detail, the hypothesis was that ACT-128800 increases vascular permeability and results in leakage of liquid and plasma proteins to the lung interstitium, which in turn attracts alveolar macrophages for clearance. Lung weights were increased starting from day 1 after administration, and no further increase in lung weights was observed from day 3 until the end of the treatment period at day 7. Histopathologic investigation revealed distension of perivascular spaces containing macrophages and eosinophils in animals treated with ACT-128800. The distension was most pronounced 3 to 10 hours after treatment and decreased again at 24 hours. In addition, the expansion appeared to be more distinct after single treatment than after seven treatments, whereas alveolar macrophages were only present after seven treatments. Administration of FITC-labelled albumin 15 minutes prior to termination of the experiment revealed leakage of the marker to the perivascular space and uptake by perivascular macrophages in ACT-128800 treated animals. In contrast, no fluorescence signal was detected in the alveolar space or in alveolar macrophages. Minimal increased alveolar histiocytosis became apparent after 7 days. Overall, lungs appeared to adapt to ACT-128800 in terms of reduction of interstitial oedema upon prolonged treatment and no effect on airways was established under the experimental conditions.

In addition to standard safety pharmacology investigation of the respiratory system, mechanistic investigations were triggered by observations of alveolar histiocytosis in rats and dogs at doses ≥ 10 mg/kg/day for 4 weeks and occasional cases of dyspnoea observed during clinical studies. The involvement of S1P in airway function has been initially assumed when bronchoalveolar lavage of asthmatic patients was found to contain increased levels of S1P as compared to healthy patients (Ammit et al., 2001). S1P mainly acts on airway smooth muscle cell contraction as well as proliferation and overall promotes a Th2 response and, thus, allergic disease (Ryann et al., 2008).

Exposure of different sections of rat tracheae to ACT-128800 (Study #B-05.080) in a protein-free buffer system revealed that ACT-128800 contracted both, upper and lower segments, in a dose-dependent manner at concentrations of 100 nM and 1 µM. ACT-128800-mediated effects were inhibited by addition of an $S1P_3$ antagonist, whereas no change in contraction was observed in the presence of an $S1P_1$ antagonist. The results suggest that ACT-128800 induces tracheal contraction via $S1P_3$ receptors. Of note, the applicant argues that due to the high protein-binding property of ACT-128800 sufficiently high concentrations to mediate this effect also in vivo are very unlikely to be achieved upon therapeutic doses.

In a second study on isolated rat tracheae, it was found that ACT-128800 at a concentration of 100 nM induces predominantly in the lower tracheal segment and not in the upper segment (Study #B-08.458). Receptor mRNA analysis revealed that $S1P_1$ and $S1P_3$ mRNA was equally expressed in the upper tracheal part, whereas a clearly higher expression of $S1P_3$ mRNA was detected in the lower part. These results confirm that ACT-128800 mediates its contractile effect on tracheae via the $S1P_3$.

Ex vivo studies on isolated human bronchi (Study #B-16.031) demonstrated that ACT-128800 is able to induce contraction at all concentrations tested, starting from 0.03 nM.

Potential effects of ACT-128800 on the CNS were investigated in a GLP-compliant modified Irwin screen in Wistar rats. A significant decrease of animals showing an increased pain response after 2 hours after dosing (30 mg/kg), as well as non-significantly increased vocaliaation (10 and 30 mg/kg), were observed. As these findings were not dose-dependent and also found in control animals ACT-128800 was concluded to not have effects on the CNS.

Pharmacodynamic drug interactions

Not provided by the applicant.

2.3.3. Pharmacokinetics

The applicant conducted an extensive non-clinical programme to assess the PK of ponesimod. Validated analytical techniques were used to determine pharmacokinetic endpoints in these studies.

The bioanalytical method used for non-clinical PK evaluations was liquid chromatography coupled to mass spectrometry (LC-MS/MS). Method validation reports for the analysis of ponesimod in the plasma of the various animal species used in the submitted development programme were provided and were considered acceptable. In addition to LC-MS/MS, studies were also conducted with radiolabelled ponesimod ([14C]ponesimod) and M13 (tritium-labelled, [3H]M13). Sufficient description of the radiochemical methods used in non-clinical PK studies (liquid scintillation counting (LSC), quantitative whole-body autoradiography, high-performance liquid chromatography (HPLC) with in-line radioactivity detection or coupled with fraction collection and LSC) were provided in the respective study reports.

Non-specific binding of ponesimod and its metabolites to plastics was demonstrated and described in selected in vitro studies (e.g. Study FK13518, FK13542). The recoveries of the added concentrations in these studies were consequently low and only matched the targeted concentrations when non-specific

binding to plastics was corrected. As *in vitro* studies constitute a pivotal contribution to the non-clinical assessment of pharmaceuticals (especially PD and PK, but also toxicity endpoints such as genotoxicity), the applicant was invited to provide information whether loss of ponesimod and its metabolites via non-specific binding to plastic laboratory utensils and lab consumables was consistently evaluated and considered in the conduct and evaluation of *in vitro* studies. The applicant provided a concise discussion that demonstrated that binding of ponesimod to plastic ware did not impact the gathered *in vitro* results to a relevant extent.

Non-dose proportionality was frequently observed in many of the animal studies conducted with ponesimod, whereby less than dose proportionality, but also greater than dose proportionality were observed. Upon request, the applicant described that non dose-proportionality in rats was presumably related to saturation of clearance at high doses, and in dogs to food intake. Furthermore, the applicant described that the non-dose proportionality in animals was not observed in humans.

Absorption was assessed in designated studies, and in toxicokinetic evaluations of toxicity studies. Regarding the former, the applicant studied *in vitro* permeability and transepithelial transport of ponesimod in the Caco-2 model (Study B-05.105, DD19014 and FK13518). Furthermore, absorption was studied in a preliminary single administration study in rats and dogs (Study B-05.074). Finally, absorption was investigated in the various toxicokinetic assessments included in toxicity studies. A separate study, however, was conducted to evaluate the toxicokinetics of the two most prominent metabolites of ponesimod, M12 and M13 in rats, dogs and mice (Study B-10.471). Time at maximum plasma concentration (t_{max}) of both metabolites was reached within hours (faster in rats than dogs), and maximum observed plasma concentration (C_{max}) and area under the concentration-time curve from time 0 to infinity with extrapolation of the terminal phase (AUC_{inf}) were similar in the fed and fasted state.

The non-clinical absorption studies indicated that ponesimod demonstrated moderate permeability and was not subject to efflux in the Caco-2 cell monolayer model, suggesting good absorption in the human intestine. In male rats and dogs, clearance did not exceed one-third of liver blood flow, volume of distribution at steady state (Vd_{ss}) exceeded total body water, and $t_{1/2}$ was faster in rats than dogs. Females generally demonstrated higher systemic ponesimod exposures (and had lower clearance and longer elimination half-lives [$t_{1/2}$'s]). Oral bioavailability was 35-53% in male rats, 61% in female rats, and 57-74% in male dogs.

Distribution was studied by *in vivo*, and *in vitro* approaches in six studies. At first, the applicant studied tissue biodistribution in the male rat by quantitative whole-body autoradiography (Study B-06.066). Tissue biodistribution in rats was also studied in the frame of *in vivo* metabolism and excretion studies in rats (see below). Then, the applicant investigated *in vitro* binding to plasma proteins and plasma/blood cell partitioning in rat, dog (the two main non-clinical species) and man (Study B-05.075, B-11.175 and B-12.195), and binding of ponesimod to human albumin and alpha 1-acid glycoprotein (Study FK13292). Finally, the applicant studied the binding of ponesimod to rat liver homogenate (Study FK13291). The placental transfer was assessed in the reproductive and developmental toxicity studies (discussed further below).

The results of the submitted distribution studies suggest that ponesimod is widely distributed into most rat tissues (including the brain) and concentrations in blood were generally lower than those in tissues. Tissue distribution of radioactivity in pigmented rats was slightly higher (~3x) as compared to corresponding tissues in albino rats. Plasma protein binding of ponesimod and M13 was high (98.9-99.6% and 99.0-99.6%, respectively) and concentration-independent in human and animal species. Uptake into blood cells was low.

In the rat whole-body autoradiography study, ponesimod was found to bind to pigmented tissues (uveal tract, nasal mucosa and skin) (Study B-06.066). Ponesimod concentrations in pigmented rats' skin and

nasal mucosa increased from day 1 to day 7 of the study (106 vs 66 ng/g and 25 vs 30 ng/g, respectively). Apart from skin and nasal mucosa, radioactivity in the pigmented rat at 7 days post-dose rat was also detected in more than half of the analysed tissues (24 analysed organs were positive, 20 analysed organs were negative), including inner organs (e.g. kidney, liver, lungs, blood, testis and epididymis, adrenal cortex, etc.) in which pigmentation and consequently binding to melanin is presumably less relevant. After 7 days post-dose in the non-pigmented rat; however, only the kidney, liver, spleen and skin contained radioactivity. The applicant clarified that distribution into pigmented tissues such as uveal tract and skin in the pigmented rat would create transient peripheral reservoirs of radiolabelled ponesimod, not present in the albino rat, that would then redistribute back into the blood and perfuse other organs during the elimination phase. This likely underlies the residual detection of radioactivity in non-pigmented tissues within the pigmented rat at Day 7.

Ulcerations and papillary hyperplasia were found in the skin of dogs in study T-08.357. Furthermore, a case of malignant melanoma and two cases of basal cell carcinoma (0.4%) were reported in the OPTIMUM clinical study. Considering that the skin enables accumulation of ponesimod (presumably by melanin-binding, Study B-06.066), a correlation between increased and prolonged ponesimod skin exposure and the skin lesions in dogs and sporadic cutaneous carcinogenesis in clinical trial participants was originally considered possible. However, the applicant replied to this concern that the dermal lesions reported in dogs receiving ponesimod were neither preneoplastic nor neoplastic and are not related to the pathogenesis of the skin malignancies seen in humans receiving S1P modulators.

Metabolism of ponesimod has been extensively studied *in vitro* and *in vivo*. The chemical structures and quantities of metabolites in biological samples were assessed in *in vivo s*tudies with radiolabelled and non-radiolabelled ponesimod. Regarding the latter, structural elucidation of circulating metabolites of ponesimod was conducted by liquid chromatography combined with high-resolution mass spectrometry (Study B-07.055). Studies with radiolabelled ponesimod included metabolic profiling studies in the rat (Study B-05.109) and in the beagle dog (Study B-06.103). *In vitro* metabolism studies were conducted to obtain cross-species comparisons of metabolic profiles. Studies with liver microsomes and hepatocytes from rat, mouse, monkey, dog, minipig and man were conducted (Study B-05.108). Furthermore, a study was initiated to elucidate whether the metabolite M1 is a real metabolite or an artefact induced by ambient light (Study B-08.379). Then, the metabolic profile of ponesimod was determined in rat liver S9 fractions (Study B-08.213). Enzyme identification and mechanistic metabolic pathway studies were conducted to identify the human enzymes (e.g. CYP450s, uridine diphosphate glucuronosyltransferases (UGT), aldehyde-dehydrogenases, aldo-keto-reductases, prostaglandin dehydrogenases) involved in ponesimod metabolism (Study B-18.004, FK12520, FK13537). Finally, mechanistic investigations on the metabolic pathways of ponesimod were conducted (Study B-16.027).

The conducted metabolism studies suggest that prior to excretion, ponesimod is extensively metabolised *in vivo* in both rats and dogs (and humans). Metabolism of ponesimod follows multiple pathways, primarily: direct glucuronidation (catalysed mainly by UGTs 1A1 and 2B7), partially CYP450-mediated (CYPs 2J2, 3A4, 3A5, 4F3A, and 4F12) oxidation through a glyceraldehyde transient intermediate to form the carboxylic acid metabolite M12, and non-CYP450 mediated oxidation to form the carboxylic acid metabolite M13. M12 and M13 were detected in plasma, urine, and bile of both the rat and dog. In humans, M13 was the most prominent metabolite in plasma (the only metabolite circulating in human plasma at ≥10% of total drug-related material), and M12 constituted the most prominent metabolite in excreta (reaching approximately similar levels as unchanged excreted ponesimod).

As both M12 and M13 are practically pharmacologically inactive, enzyme polymorphisms leading to an altered turnover of ponesimod could cause over- or under-exposure of the active parental substance. This could lead to either decreased pharmacological efficacy (rapid metabolism and therefore under-exposure of ponesimod) or increased secondary pharmacology/exaggerated pharmacology (slow

metabolism and therefore over-exposure of ponesimod). Addressing this concern, the applicant concluded that there is no evidence from the conducted *in vitro* studies of an important role for polymorphic enzymes in the metabolism of ponesimod. Furthermore, the applicant stated that ponesimod metabolic clearance involves multiple independent pathways, each with multiple enzymes contributing. Finally, the applicant argued that clinical PK features support the lack of clinically relevant polymorphic enzymes involved in ponesimod clearance. Considering these aspects, the potential impact of enzyme polymorphisms on the PK of ponesimod indeed appears negligible.

Excretion endpoints were studied separately or included in *in vivo* metabolism studies in intact rats and bile-duct cannulated rats and dogs after single and dose oral or intravenous administration (Study B-05.109, B-06.103 and B-06.003). Excretion of ponesimod in milk was studied in the preliminary and pivotal rat PPND studies (see below).

The results of the conducted excretion studies suggest that hepatobiliary excretion of systemic ponesimod prevails, whereas renal excretion represented only a minor elimination pathway in rat and dog both species (<10% of the dose). Some of the systemic ponesimod was also directly secreted into the intestines. Radioactivity associated with ponesimod exposure was also exhaled to a minimal extent (in the per-mill range). In rats and dogs, a limited first-pass effect is conceivable (approximately 10% of administered ponesimod).

Finally, the applicant carried out a broad panel of *in vitro* PK drug interaction studies to investigate potential enzyme induction and inhibition as well as transporter inhibition by ponesimod. At first, metabolism-mediated drug interactions were studied by assessing the inhibition potential of human cytochrome P450 and UGT enzymes by ponesimod (Study B-05.078, B-13.080 and FK13543). Time-dependent inhibition of CYP450 activity by ponesimod was studied for CYP3A4 and CYP2C9 in Study B-08.581, and for CYP1A2, 2B6, 2C8, and 2C19 in Study FK13536. Induction of drug metabolising enzymes by ponesimod (and M13) was studied *in vitro* for human cytochrome P450s (Study B-08.466 and Study B-17.003), and in cultured human hepatocytes (Study FK13519). Finally, the applicant studied whether ponesimod and M13 are transporter substrates and/or transporter inhibitors. Regarding the former, transporter-mediated drug interactions by ponesimod (and M13) were studied on breast cancer resistance protein (BCRP) in MDCKII cell lines overexpressing this transporter (Study FK13542), and on organic anion transporting polypeptide (OATP)1B1- and OATP1B3-mediated transport (Study FK13541). Regarding ponesimod and M13 as transporter inhibitors, the inhibition potential of ponesimod and its metabolite M13 on the activity of the human uptake transporters OATP1B1, OATP1B3, OAT1, OAT3, Organic Cation Transporters (OCT)1 and OCT2 and the human efflux transporters multidrug and toxic compound extrusion (MATE)1, MATE2K, P-glycoprotein (P-gp) and BCRP was studied (Study B-14.025).

These studies demonstrate that ponesimod had an inhibitory effect on the activity of CYPs 2C19, 2C9, 2C8, 2D6, 2J2, and 3A4, with half-maximal inhibitory concentration (IC_{50}) values from 7.8-36 µM, whereas inhibition was <50% for the other isoforms at the highest tested concentration (50 µM except 100 µM for CYP2A6). M13 inhibited the activity of CYPs 2C8, 2C9, and 3A4 in human liver microsomes, with respective IC_{50} values of 9.7, 43, and 20 µM, whereas 50% inhibition was not attained for the other isoforms at the highest tested concentration of 100 µM (CYPs 1A2, 2A6, 2B6, 2C19, and 2D6). Neither ponesimod nor M13 showed evidence for time-dependent inhibition of evaluated CYP450s. UGT2B7 activity was inhibited by ponesimod and UGT1A1 activity by M13, with respective IC_{50} values of 17 and 24 µM. Based on a combination of static and physiologically based pharmacokinetic modelling, the applicant determined that the observed *in vitro* inhibition findings do not indicate a clinically relevant inhibition risk for any of the CYPs or UGTs evaluated. Similarly, enzyme induction by ponesimod was discussed to be unlikely at therapeutically achievable concentrations.

BCRP and the hepatic uptake transporters OATP1B1 and OATP1B3 were inhibited by both ponesimod and M13. For renal uptake and efflux transporters, OAT1 and OAT3 were inhibited by M13, MATE1 by

ponesimod, and MATE2K by both ponesimod and M13. Less than 50% inhibition was attained at the highest tested concentration for P-gp and MATE1 by M13, OAT1 and OAT3 by ponesimod, and OCT1 and OCT2 by both ponesimod and M13. Based on static modelling and additional analysis, the applicant determined that the observed *in vitro* transporter inhibition findings do not indicate a clinically relevant inhibition risk for any of the transporters evaluated.

Even though M13 is the most abundant metabolite of ponesimod in human plasma, M12 was more than 5 times as abundant as M13 in human excreta. M12 almost even reached the levels of unchanged ponesimod in human excreta. Biliary excretion of systemic ponesimod and metabolites is considerable higher in humans and animals than urinary excretion. Considering these points, one can assume that the liver experiences equal or perhaps even higher M12 than M13 concentrations. Therefore, assessing enzyme inhibition, enzyme induction, and transporter inhibition by M12 instead of M13 might have been a better choice. However, in response to this concern, the applicant cautioned that the formation and elimination kinetics of the metabolites of ponesimod cannot be solely understood from excreta recovery data and that, therefore, excretion data should not be taken as a surrogate for intrahepatocellular drug and metabolite concentrations. The applicant substantiated this statement by the radio profile of [14C]ponesimod metabolites in the rat bile, which demonstrated equal biliary M12 and M13 levels.

Originally it was not clear whether inhibition of CYP2J2 could decrease turnover rates (and subsequently decrease excretion rates) of the pharmacologically active ponesimod into the pharmacologically less-active M12. A lower turnover of ponesimod because of CYP2J2 inhibition could theoretically lead to exaggerated pharmacology and related adverse effects. However, the applicant replied to this concern that quantitative contribution of CYP2J2 to ponesimod metabolic clearance *in vivo* is expected to be low and that, thus, inhibition of CYP2J2 by co-administered compounds would not be expected to have clinically relevant impact on ponesimod exposure.

In study FK13541, ponesimod was not a substrate of OATP1B1 and OATP1B3; however, it inhibited the uptake of 3H-Egluc in both OATP1B1 and OATP1B3 transfected cells. It was not clear how ponesimod inhibited the uptake of 3H-Egluc when at the same time not being a substrate of the two transporters. The applicant was consequently expected to discuss this discrepancy. However, the applicant described that the observed discrepancy could theoretically also be accounted to allosteric OATP1B inhibition by inhibitors or to post-translational modifications or interactions between the inhibitor and the transporter at the inner leaflet of the plasma membrane. Relevant literature was provided on these speculations. Therefore, the concern was considered resolved.

2.3.4. Toxicology

The applicant conducted an extensive non-clinical programme to assess the toxicology and environmental risk of ponesimod. All pivotal studies were conducted in GLP compliance.

Single dose toxicity

No single dose toxicity studies were carried out, as lack of toleration was already observed in dose-range finding studies in rats and in dogs. This is acceptable.

Repeat dose toxicity

The applicant submitted an extensive repeated dose toxicity programme in rats and dogs. However, note that also a dose-range finding study (non-GLP) was conducted with cynomolgus monkeys (Study T-

08.427). Regarding the submitted rat and dog repeated dose toxicity studies (RDTS) programme, the applicant conducted the following studies:

- Rats: 3 days maximum tolerated dose (MTD) study (Study T-05.018), 14 days dose range finding (DRF) study (Study T-05.019), 2x4 weeks studies with 4 weeks recovery (Study T-05.043 and T-05.129), 26 weeks study with 13 weeks recovery (Study T-05.134);
- Dogs: DRF study (Study T-05.020), 2x4 weeks studies with 4 weeks recovery (Study T-05.042 and T-05.148), 26 weeks study with 13 weeks recovery (Study T-05.139), 13/26 weeks with daily and bi-daily dosing (Study T-07.186), 52 weeks study with 13 weeks recovery (Study T-06.186), 52 weeks MTD study (Study T-08.357).

The extent of this programme is considered sufficient to support an MAA of ponesimod. Repeated dose toxicity was also studied in mice (to obtain preliminary data for carcinogenicity studies) and to a certain extent in rabbits (to obtain preliminary data for embryo-foetal development (EFD) studies). The following RDST were conducted with mice and rabbits:

- Mouse: 14 days DRF study (Study T-05.128), 2x13 weeks studies (Study T-06.049 and T-07.015);
- Rabbit: 14 days DRF study (Study T-05.111).

Repeated dose toxicity studies performed in rats, dogs, and mice identified the lung (mouse, rat, dog), heart (dog), nervous system (clinical signs, dog), skin (dog), red blood cell (RBC) compartment (rat), liver (mouse, rat, dog), adrenals (rat), kidney/brain (rat; carcinogenicity study) and lymphocytes/lymphoid organs (mouse, rat, dog), as the main organs affected by treatment with ponesimod. The effects of ponesimod on the lung, the heart and the CNS were further characterised in dedicated safety pharmacology studies; therefore, no concerns were raised on the toxicity on these organs. Some other organs might also be affected, which is the content of selected other concerns on the toxicology of ponesimod. It should be noted that for monkeys only a non-GLP tolerability study is available which has limited group sizes and does not include histopathological examination, so only limited conclusions can be drawn from this study and for this species.

The applicant derived no observed adverse effect level (NO(A)EL)s for systemic toxicity at 2 mg/kg/day in rats and at 0.4 mg/kg/day in dogs after 4 weeks of treatment. After chronic treatment for 26 weeks, NOAELs for systemic toxicity were established at 30 mg/kg/day in rats and at 2 mg/kg/day in dogs. In the 52-week toxicity study in dogs, the applicant derived a NOAEL at 3 mg/kg/day. Significant toxicity observed in rats at doses of 400 mg/kg/day and in dogs at doses ≥75 mg/kg/day led to unscheduled necropsy of animals and/or dose reduction.

A study on the combinatory repeated dose toxicity of ponesimod and dimethyl fumarate in dogs was submitted (Study T-14.019). As this combination is not within the applied indication of this MAA, only the results obtained from the ponesimod-alone groups of this study were assessed.

A number of other concerns were originally raised during the procedure with regards to the RDTS programme.

In many animal toxicity studies, clearly decreased plasma transaminase levels (statistically significant) were observed. The relevance of this finding was originally not discussed. However, the applicant demonstrated (by referring to adequate literature) that the scattered decreases in plasma transaminase levels in the conducted toxicology do not bear relevance.

In many animal studies, increased platelet counts relative to control group values were observed in animals of test-article groups. These findings were originally not sufficiently discussed. The applicant, however, provided a sufficiently detailed discussion on this finding and concluded that, based on the lack

of e.g. increases in prothrombin time (PT), activated partial thromboplastin time (APTT), adverse bone marrow changes and clinically increases in platelets, this finding also bears no relevance. This position was supported.

Direct (organ weights and macroscopic/histological alterations) and indirect (clinical chemistry) liver effects in animal toxicity studies could be attributed to the administration of ponesimod. The applicant speculates that liver effects in test-article groups were non-adverse and reflect metabolic adaptations to ponesimod administration. However, in some animal toxicity studies, direct or indirect liver effects were not fully reversible after the recovery period, indicating that ponesimod could have induced permanent hepatotoxic effects. Upon request, the applicant provided an adequate discussion on the relevance of the observed liver alterations in animal studies and attributed them to non-adverse change in the liver due to drug-induced enzyme induction. In rats and dogs, the applicant argued that no corresponding increases in plasma transaminase levels were observed, further supporting the non-adversity of these findings. At very high doses in mice, the observed focal hepatocellular necrosis and slight increases in alanine aminotransferase (ALT) can – according to the applicant – also be accounted to excessive hypertrophy from enzyme induction. The totality of data, therefore, indicates that the observed liver alterations bear little relevance.

In some animal studies, prostate weights in test-article groups were altered relative to control group weights (statistically significant). Originally, the applicant did not elaborate on these findings, but only concluded that these alterations were not test-article related. During the procedure, the applicant provided a useful discussion and concluded that the relevance of the lower prostate weight in the 26-week dog study is considered low as this alteration was only noted at high exposure, not reproduced in the 52-week dog-study at similar exposures, and as no related microscopic findings in the male reproductive tract across the non-clinical studies observed. Furthermore, the applicant argues that in beagle dogs, there can be a high inter-individual variability in prostate weight (this could indicate that the observed alterations in prostate weights might indeed be chance findings). Considering these points, the prostate alterations occasionally observed in dog studies unlikely bear relevance for patients.

In study T-08.427, as the dose increased 100-fold in female cynomolgus monkeys from 10 to 1000 mg/kg/day during the ascending dose phase, the C_{max} and area under the concentration-time curve in a dosing interval of 24 hours (AUC_{0-24}) increased 5.2 and 6.4 fold, respectively. This is a considerably low increase in area under the concentration-time curve (AUC) and C_{max} given the 100-fold increase in dose. Originally, the applicant was asked to elaborate on this issue. However, the applicant refused to answer this question accordingly, as this cynomolgus monkey study was only an exploratory non-GLP compliant study. As this study was only a non-pivotal study, this issue was no longer pursued.

Genotoxicity

Genotoxicity was studied in a standard battery of *in vitro* assays and *in vivo* tests, including Ames assays of ponesimod (Study T-05.058) and its two most important metabolites M13 (Study 09.519) and M12 (Study T-09.520), an *in vitro* chromosome aberration assay using cultured human peripheral blood lymphocytes (Study T-05.064), and an *in vivo* micronuclei assay in rats (Study T-07.143). The submitted genotoxicity programme adheres to the guidance given in the respective ICH S2(R1) document, no additional studies are required.

In study T-05.064, small increases in the frequency of cells with numerical aberrations in test-article groups (above the historical control range) were observed. However, not a single numerical aberration was observed in the control groups of experiment 1 & 2, whereas sporadic numerical aberrations were observed in most treatment groups, albeit they never followed a dose-response trend. As the treatment of MS requires a chronic administration of ponesimod, the applicant was expected to provide a more

detailed discussion on the observed sporadic increases of numerical aberrations in human lymphocytes observed in this study relative to control groups (in which no numerical aberrations were found at all). The applicant clarified that these sporadic increases seen under some test conditions were not reproducible (confined to single culture), not statistically significant and that there was no dose-relationship. The few numerical aberrations can therefore be considered a random chance finding.

The Ames test did not show a mutagenic potential for ponesimod as well as M12 and M13. The *in vitro* chromosome aberration test demonstrated a slight (and potentially negligible) tendency of ponesimod to induce aneugenicity, whereas clastogenicity was not observed. The *in vivo* rat micronucleus did not demonstrate test-article related effects on micronuclei formation.

Carcinogenicity

Carcinogenicity of ponesimod was assessed in a long-term two-year mouse (Study T-13.023) and rat (Study T-13.024) study. This submitted carcinogenicity programme is in line with the recommendations given in the ICH M3(R2) guidelines and is therefore acceptable.

In mice, the incidence of neoplastic vascular tumours (haemangiosarcomas, and the combination of haemangiosarcomas and haemangiomas) was statistically significantly increased in test-article groups when compared to concurrent controls. The incidence of spontaneous haemangiosarcomas ranged from 2-12% in the historical control data of the respective contract research organisation. In study T-13.023, the combined incidence of haemangiosarcomas and haemangiomas was 12-25% in ponesimod-treated mice, in contrast to 2-10% in the control groups. Therefore, this increased incidence was without doubt related to the administration of ponesimod. However, the applicant argued and provided literature that the spontaneous incidence of haemangiosarcomas in humans was reported to be 0.00021%, but high in mice (e.g. 2-10% in the control groups of this study), indicating that humans are substantially less susceptible to developing these tumours than mice are. The applicant further speculates (by referring to adequate literature) that the high background incidence of haemangiosarcomas and haemangiomas in mice is considered to be related to a species-specific higher rate of endothelial cell proliferation as compared to rats or humans. In this setting, the applicant speculates that ponesimod acts as a mitogen and increases vascular proliferation rates, which leads to tumour formation and in the end carcinogenesis. The applicant states that similar findings have been described in the mouse carcinogenicity study with the S1P modulators fingolimod and siponimod, indicating that this could be a class effect of S1P modulators in mice. In rats (Study T-13.024), ponesimod did not induce test article-related neoplastic lesions. In general, the applicant's positions were considered plausible; however, also in dog repeated dose toxicity studies, vascular arterial lesions were observed that could theoretically be promotive for tumorigenesis. These arterial lesions were characterised by hypertrophy and hyperplasia of smooth muscle cells in the tunica media and, more pronounced at 40 mg/kg/day, by the development of multiple vascular channels within the hypertrophic media and the luminal side of the internal elastic lamina. This could indicate that ponesimod acts as a mitogen in dog vasculature. Considering these aspects, the applicant was invited to elaborate on these aspects. During the procedure, the applicant responded to these questions that in the mouse, endothelial cells are the primary affected cell type and considered the result of an $S1P_1$ mediated increase in endothelial cell proliferation, whereby in the dog the arterial smooth muscle cells are mainly affected, secondary to $S1P_3$-mediated vasoconstriction and subsequent haemodynamic changes, resulting in exaggerated arterial adaptation/remodelling. The applicant further specified that the vascular lesions in the dogs were secondary to hemodynamic changes/ischemia and are not preneoplastic, and no risk factor for neoplasia. Regarding the molecular mechanisms of the observed haemangiosarcomas and haemangiomas, the applicant specified that these neoplasms are a species-specific effect in mice possibly related to increases in vascular endothelial cell

activation and proliferation associated with the release of the pro-angiogenic factor, placental growth factor (PLGF2), and not relevant to human. This interpretation is endorsed.

In study T-13.024, the applicant speculates that the observed brain mineralisations in this study were caused by a disturbed Ca homeostasis in test article groups. However, no relevant Ca alterations were observed in plasma in clinical biochemistry investigations. As this effect was highly dose-dependent (and was maximally observed in 1 out of the 51 animals in both control groups of both sexes), it originally was not considered likely that brain mineralisation was an age-related background finding. However, the applicant responded to this concern that brain mineralisation was reported only in rats and was not observed in other preclinical species (dogs and mice) and provided literature that demonstrates that other S1P modulators also increased the incidences and severity of brain mineralisation in aged rats but not in other preclinical species. Considering these points, the observed mineralisations in geriatric rats are most likely a species-specific finding with no relevance for the clinical use of ponesimod.

The uterus weight of female rats was clearly increased in test-article groups of the T-13.024 Study. This observation even achieved an increase of almost a factor three relative to control values, suggesting that increased uterus weights were not a result of normal menstrual cyclicity. In addition, the incidence of uterus distension was increased in high dose groups, following a dose-response relationship. Furthermore, the incidence of macroscopically observed thick uteri was increased in test-article groups. Also, ovary cysts were observed in females of intermediate and high treatment groups in a dose-dependent fashion, but not in the two-vehicle groups. To a lesser extent, macroscopic alterations of the ovaries were also exclusively attributable to test-article groups, and not to the two control groups. The applicant argued and provided literature that demonstrated that geriatric animals are not a good indicator for non-neoplastic effects on the female reproductive tract. Considering this, the applicant cautioned to interpret non-neoplastic findings in old rodents in carcinogenicity studies (such as this study). Finally, the applicant argued that there was no clear dose-relationship and no correlation with test-article related microscopic findings of the female reproductive tract. Considering these points, it indeed appears that the observed findings could be a chance finding.

In study T-07.015, even up to 800 mg/kg/day, there was no consistent decrease in lymphocyte counts in mice after 13 weeks of administration. Therefore, it appears that ponesimod was not sufficiently pharmacologically active in mice. However, decreased lymphocyte counts were found in mice at sub-acute exposure (Study T-05.128). Given the discrepancy between sub-acute and chronic dosing, and the fact that chronic administration of considerably high ponesimod doses did not show consistent effects on the lymphocyte counts, the applicant was expected to discuss if the mouse is susceptible to the PD of ponesimod at chronic exposures, and whether the mouse is a relevant non-clinical species for long-term studies (especially in regards to the conducted carcinogenicity study). The applicant responded to this concern that the absent decrease in lymphocyte counts in mice after 13 weeks of in Study T-07.015 24 hours post-dose could be related to the high clearance of ponesimod in the mouse and the consequent rapid fading of the pharmacological effect (in terms of decreasing peripheral lymphocytes). This justification was found to be plausible.

Reproduction Toxicity

The applicant conducted an extensive non-clinical programme to assess the reproductive and developmental toxicity of ponesimod. The following studies were conducted:

- Segment I: Fertility and early embryonic development studies in female (Study T-07.109) and male (Study T-08.429) rats;

- Segment II: DRF (Study T-05.110) and pivotal (Study T-06.093) EFD studies in rats, DRF (Study T-06.074) and pivotal (Study T-06.075) EFD studies in rabbits;
- Segment III: DRF (Study TOX13421) and pivotal (Study TOX13502) pre- postnatal developmental toxicity (PPND) study in rats;
- Juvenile toxicity: DRF (Study T-15.063) and pivotal (Study T-16.018) juvenile toxicity study in rats.

This programme suffices the guidance given in the ICH M3(R2) and the ICH S5(R3) documents. Therefore, the applicant's programme on reproductive and developmental toxicity is considered adequate to support a potential MA. Note that because of the EFD study results, the applicant defined a contraindication for pregnancy in the Summary of product characteristics (SmPC).

In the female fertility study in rats, fertility appeared to be largely unaffected by treatment at doses up to 100 mg/kg/day. There was no effect on early pregnancy parameters. In the male fertility study, mating and fertility were unaffected by treatment at doses up to 100 mg/kg/day. The applicant claims that no effects were observed on male reproductive organs in the male fertility study. However, statistically significant decreases (below the historical control range) in sperm counts were observed in testes (all three ponesimod groups) and epididymides (low and intermediate ponesimod group) of rats in study T-08.429. The applicant claims that these findings were incidental due to the absence of a dose-dependency and morphological and microscopic observations. The fact that no dose-response was observed among the affected treatment groups does not necessarily imply that these findings are not treatment related: (i) first, systemic exposure to ponesimod was frequently less than dose-proportional, indicating that a dose-relationship, in that case, would not be as extensive as derived from the applied dosing regimens and (ii) second, the potential adverse mode of action of ponesimod, leading to a decreased sperm count in testes and epididymides could have already been saturated at the lowest dose administered (10 mg/kg/day). In this case, an increase in dose would not lead to an increased severity of the observed effect. Furthermore, the applicant's claim of absent macroscopic and microscopic correlates to decreased sperm counts in this study was originally not fully supported, as increased testes/BW ratios were observed in all three treatment groups of this study (attaining statistical significance only at the 10 mg/kg/day dosing regimen). Additionally, in the rat 14 days repeated dose toxicity study T-05.019, cellular debris in the epididymides were observed at the highest dosing regimen, indicating that ponesimod is also capable of inducing microscopical alterations in the gonads of male rats. Considering these points, the applicant was invited to thoroughly discuss the observed decreased sperm counts in this study and propose a potential aetiological relation of this observation with ponesimod exposure. Finally, the applicant was expected to discuss whether decreased sperm counts are a known class effect of other S1P modulators, or whether the impacts of S1P modulators on male fertility have been assessed in other non-clinical species or male patients. The applicant responded to these concerns that the observed changes were minor (<15%) and without biological relevance. The applicant further specified that a decrease of >20- 25 % in sperm counts in rats is needed before being considered biologically relevant. Due to this estimation and because of the absence of a pathological correlate and dose- relationship, the concern was considered as being resolved.

The EFD studies in rats showed marked embryofoetal toxicity in which embryofoetal survival, growth, and morphological development were severely compromised at 40 mg/kg/day. Teratogenic effects with malformations of the limbs and the cardiovascular system (including ventricular septum defects) were observed at doses ≥10 mg/kg/day. A NOAEL for embryofoetal toxicity/teratogenicity in rats was claimed by the applicant at 1 mg/kg/day. The rabbit even appeared more sensitive towards ponesimod-related EFD-disruption than the rat. EFD studies in rabbits showed an increase in post-implantation loss after dosing at 4 mg/kg/day. Foetal findings consisted of an increased incidence of foetuses with fused sternebrae and additional minor blood vessels arising from the aortic arch. The applicant claims that the

embryofoetal NOAEL in rabbits was 1 mg/kg/day. In the PPND studies, dosing of mated (F0) female rats at 20 mg/kg/day led to a slightly lower viability index of pups from birth to postnatal day (PND)4. The F1 pups had slightly lower BW and BW gains at 20 mg/kg/day, and F1 females showed a lower fertility rate at 20 mg/kg/day. Sexual maturation was delayed in F1 males and females of all groups.

Interestingly, no effects on sexual development, fertility and pregnancy were observed in the pivotal juvenile toxicity study (Study T-16.018), contrasting the delayed sexual development and lowered female fertility observed in the F1 generation in the pivotal PPND study (Study TOX13502). This could suggest that ponesimod exposure during early development (PPND) may irreversibly alter the development of the reproductive system, whereas post-weaning exposure during juvenile development does not. The applicant was expected to elaborate on these irreversible alterations in the offspring that were exposed. In response to this question, the applicant suggested that it was maternal toxicity that caused the developmental toxicity, and that consequently such effects were not observed in the juvenile toxicity study in which the offspring was directly dosed. Furthermore, the applicant stressed that the observed effect on F1 fertility in the PPND study is appropriately mentioned in the SmPC.

F1 pups were noted to have ponesimod in the plasma on lactation Days 4 and 12 which would indicate ponesimod exposure to pups via the milk of the lactating dam. At 20 mg/kg/day of maternal dose, the F1 pup exposure levels were approximately 0.2-fold of the expected clinical exposure at 20 mg daily. These findings were included in the SmPC. Recommendation that women receiving ponesimod should not breastfeed is included in the SmPC section 4.6. In the section 5.3. information is provided that ponesimod was present in the plasma of rats F1 pups, indicating exposure from the milk of the lactating dam.

In the pivotal juvenile toxicity study, the applicant claims that the NOAEL was at 100 mg/kg/day. Based on reduced humoral immunocompetence observed at all ponesimod dosing regimens (see below) and liver and lung findings, the applicant was invited to reconsidered the claimed NOAEL at 100 mg/kg/day. As part of responses, the applicant defended the NOAEL of this study, which was defined at 100 mg/kg/day. Findings were limited to adaptive and/or pharmacological responses in white blood counts (WBC) and reticulocyte counts, lipid parameters, lymphoid organs, lung and liver and were found to be fully reversible. No delay in sexual maturation and no decreased fertility were observed.

In study T-16.018, the humoral response to antigens in adult rats (to SRBCs) in the pivotal 26 weeks repeated dose toxicity study (Study T-05.134) did not indicate an impaired humoral immunocompetence under ponesimod exposure. Contrarily, in juvenile rats, humoral immunocompetence towards the antigen KLH was partly impaired at all dosing regimens. Interestingly, humoral immunocompetence towards KLH was not clearly decreased in adult dogs in study T-14.019. Hence, partial impairment of humoral immunocompetence by ponesimod administration seems to be age-dependent and refined to non-adult animals. In response to this, the applicant discussed that while humans and nonhuman primates are born with a functional immune system, much of the rodent immune system development occurs postpartum (the applicant specified that rats still have a developing immune system up to PND70 and that T-dependent antibody response (TDARs) should therefore be assessed after PND45). Considering this, the applicant speculated that ponesimod exposure during this phase of immune development in the rat is either delaying lymphoid development or the rats may not be fully mature to be able to compensate with other antigen presenting cells. Considering these points, the decreased immunocompetence after ponesimod exposure in rats is unlikely to be relevant in patients.

Local Tolerance

Local tolerance was studied after intravenously administration of ponesimod in rabbits (Study T-13.001). No test-article related signs of local irritation were observed.

Other toxicity studies

No antigenicity studies were conducted, which is acceptable.

Similarly, no dedicated immunotoxicity studies were conducted; however, immunotoxicity evaluations (immunophenotyping and humoral immunocompetence evaluations towards sheep erythrocytes [SRBC] and keyhole limpet hemocyanin [KHL] antigen challenge) were included in general toxicity studies. Ponesimod was immunotoxic as it caused decreased peripheral WBC counts, especially affecting lymphocytes. This, however, constitutes the pharmacologic mode of action of ponesimod. Of note, especially the peripheral counts of CD4+ T cells (and to a lesser extent CD8+ T cells) were decreased in immunophenotyping studies, whereas NK cells and monocytes were generally resistant towards a reduction in peripheral blood. Humoral immunocompetence towards antigen challenge was generally not affected by ponesimod administration in adult rats and dogs but was compromised by ponesimod exposure in juvenile rats (as discussed above).

The potential of ponesimod to induce drug dependency was discussed by the applicant to be negligible. This appears plausible.

No dedicated toxicology studies were conducted with metabolites (with the exception of Ames tests), as the relevant metabolite concentrations in animal studies were above the concentrations expected in patients. As the most abundant metabolites of ponesimod (M12 and M13) are additionally hardly pharmacologically active, and are not genotoxic, the waiving of dedicated toxicity studies on metabolites is acceptable.

Studies on impurities are discussed in the Quality section.

Additionally, a phototoxicity study was submitted (Study T-05.060), which demonstrated that ponesimod could be considered as non-phototoxic.

2.3.5. Ecotoxicity/environmental risk assessment

An ERA was submitted, in which the applicant determined the K_{ow} of ponesimod (4.3) and calculated its predicted environmental concentrations surfacewater (PEC_{sw}) (0.00965 µg/L). Based on these two values, the applicant originally concluded that ponesimod does not need a persistence, bioaccumulation and toxicity (PBT) assessment, and that no phase II evaluation of ponesimod is required.

The applicant's determination of the K_{ow} of ponesimod was originally considered to be potentially erroneous. The solubility of ponesimod in water was reported to be 0.669 µg/mL at pH 5.76, in 1 litre water this would be 0.669 mg/L. In experiments for K_{ow} determination, ponesimod concentrations were however, observed up to 1.72 mg/L in water, suggesting that ponesimod was oversaturated, as the claimed solubility limit in water was surpassed by more than a factor 2. The different pH in the watery compartment in the reaction containers (which ranged between 6.24 and 6.67) relative to the solubility limit determined at pH 5.76 thereby most likely did not cause an increased solubility, as the applicant stated that no ionisation of ponesimod is predicted in the environmentally relevant pH range. Because oversaturation in the determination of K_{ow} coefficients must be avoided (as an oversaturated compartment would yield different K_{ow} coefficients at different concentrations), the applicant was invited to clarify:(i) whether the derivation of the solubility of ponesimod in water (0.669 µg/mL) as provided could have been erroneous and (ii) whether the water compartment in the K_{ow} experiment could have indeed been oversaturated with ponesimod, and if this could have influenced the determination of the K_{ow} coefficient.

The applicant indeed responded to this concern that the evaluation of the water solubility and partition coefficient of ponesimod was not conducted according to relevant quality standards. Therefore, the

applicant proposed that these studies will be newly conducted as post-authorisation measure (PAM) [REC] in 2022, whereby the applicant specifies that the studies will be conducted along with the respective Organisation for Economic Co-operation and Development (OECD) and GLP-requirements. This strategy is endorsed.

Then, the applicant's calculation of Fpen (Factor of market penetration) and consequently, PEC_{sw} was not supported. At first, using an outdated MS prevalence (90.7 in 100000) from a publication from the year 2003 for the calculation of Fpen was not considered acceptable. Then, taking the mean MS prevalence found in Europe for deriving the Fpen was also not considered acceptable, as MS prevalences considerably vary among European countries. Therefore, a more conservative approach was recommended for the derivation of the Fpen value. This can be achieved by calculating the Fpen value by using an up-to-date epidemiologic prevalence of MS of the European country exhibiting the highest MS burden (in the case of Europe this would be Denmark with 227 MS cases per 100000; Atlas of MS, 2013). Using this prevalence for the derivation of the Fpen, the PEC_{sw} of ponesimod would be 0.0227 µg/L, being clearly above the value triggering a phase II evaluation (0.01 µg/L). (Note that the indication of this MAA only includes relapsing forms of MS; therefore, derived Fpen values using a prevalence for all MS forms would, in reality, be a bit lower. However, as most forms of MS are relapsing in their nature, this effect is probably only minimal.) Considering all these points, the applicant was expected to commence a phase II evaluation. Additionally, as the K_{ow} of ponesimod is above the trigger value of 1000 L/kg, a fish bioaccumulation study, according to OECD TG 305 in Tier B was considered warranted.

The applicant agreed with the raised concerns and discussed that a phase II ERA assessment is necessary for determining the potential impact of ponesimod on the environment. Therefore, the applicant proposed that the following ERA studies (Table 2) will be conducted along respective OECD and GLP-requirements as PAM [REC] in Q4 2022.

Table 2: ERA studies to be conducted by the applicant as a post-authorisation measure

Phase II TIER A: Aquatic studies	***Janssen Study No.***	***CRO Study No.***	***Guideline***
Water solubility	RMD1296	CRL-278277	OECD 105
Partition coefficient octanol/water (log Pow)	avaliable	LAUS	OECD 123
Adsorption desorption study (Koc)	RMD1297	CRL-278278	OECD 106
Ready biodegradation	RMD1298	CRL-272381	OECD 301B
Aerobic transformation in aquatic sediment systems	RMD1299	CRL-278280	OECD 308
Activated sludge respiration inhibition	RMD1301	CRL-284751	OECD 209
Algae growth inhibition	RMD1302	CRL-272377	OECD 201
Daphnia acute toxicity test	RMD1303	CRL-272379	OECD 202
Fish Acute Toxicity	RMD1304	CRL-272380	OECD 203
Daphnia reproduction test	RMD1305	CRL-278282	OECD 211
Fish Early Life Stage test	RMD1306	CRL-278283	OECD 210
Phase II TIER B: Bioaccumulation & Terrestrial studies	***Janssen Study No.***	***CRO Study No.***	***Guideline***
Bioaccumulation test	RMD1307	CRL-278285	OECD 305
Sediment dweller *(Chironomus)* toxicity test	RMD1308	CRL-278284	OECD 218/219

This approach could be acceptable. However, the applicant is reminded that the decision whether the scope of the proposed Tier B phase II studies is sufficient depends on the results of the Tier A phase II studies. Completeness of the ERA programme will be assessed once the studies will be submitted in the frame of a variation.

2.3.6. Discussion on non-clinical aspects

The PD profile of ACT-128800 was thoroughly evaluated by *in vitro* and *in vivo* studies. ACT-128800 could be demonstrated to be an $S1P_1$ and, to a lesser extent, $S1P_3$ agonist. In vivo, ACT-128800 efficiently reduced circulating lymphocytes in healthy animals, with naïve CD4+ and CD8+ cells, as well as γδ T-cells and NKT, being the most affected subsets. In contrast to non-selective S1P agonists, upon ACT-128800 treatment lymphocyte levels returned to baseline more rapidly after cessation of treatment. ACT-128800 also proved effective in preventing the onset of or reducing clinical signs in T-cell mediated disease models.

From non-clinical safety pharmacology studies, no signs for ACT-128800 to have effects on QT interval prolongation and HR could be seen. A dose-dependent increase in BP was observed in dogs and could be related to a vasoconstrictive activity of ACT-128800 specifically mediated on canine arteries. No constrictive activity was detected *ex vivo* on human or rat arteries. With regard to respiratory function, a dose-dependent transient slight impairment was observed in rats but not in dogs. Occasional cases of dyspnoea in response to ACT-128800 treatment were also noted in clinical trials. In vitro studies revealed that ACT-128800 has a contractile effect on rat tracheae and human bronchi at supra-therapeutic concentrations. ACT-128800 was also found to increase vascular permeability in rat lungs which lead to transient perivascular oedema, alveolar histiocytosis and increase in lung weight. No notable effects of ACT-128800 on the CNS were detected. Thus, all effects detected in the scope of safety pharmacology studies are considered to have been thoroughly followed up and could be well put into the context with the pharmacologic action of ACT-128800.

The PK of ponesimod were thoroughly investigated in a wide panel of *in vitro* and *in vivo* studies. However, a number of other concerns were originally raised on non-clinical PK aspects that were not sufficiently discussed by the applicant, or that may exhibit safety concerns. These aspects were properly addressed by the applicant. In general, the PK of ponesimod have been sufficiently assessed. It exhibited a moderately well absorption, a thorough distribution into tissues, a complex metabolism, and a prevailing hepatobiliary excretion. These ADME characteristics fit the high lipophilicity of ponesimod. DDI studies demonstrated that interactions of ponesimod with concomitantly administered pharmaceuticals or other substances are unlikely at the encountered therapeutic ponesimod levels.

Toxicological investigations of ponesimod demonstrated that the non-clinical safety of this compound was similar to the safety profile of other S1P modulators. The conducted toxicology programme is considered to be adequate in terms of quantity and quality of studies. Affected off-target organs in non-clinical studies were especially the lung and the heart (at high doses also the CNS); however, the applicant sufficiently addressed adverse effects related to disturbances of these off-targets in an exhaustive safety pharmacology programme. Other off-targets affected by ponesimod administration were consistently identified in non-clinical studies and were the subject of dedicated other concerns. Similarly to other S1P modulators, ponesimod largely proved to be non-genotoxic and non-carcinogenic, observed carcinogenic effects in the mouse most likely constituted a species-specific finding that is not relevant for human patients. As identified for other S1P modulators, ponesimod was toxic to EFD; the applicant, therefore, defined a contraindication on pregnancy. Furthermore, the applicant claimed that ponesimod was not toxic to male and female fertility. Finally, developmental toxicity appears to be refined to disturbances during early ontogenesis at the PPND stage (via maternal exposure). Other modes of toxicity (phototoxicity, local tolerance, etc.) were investigated, but no relevant test-article related effects were found.

Originally, a phase I ERA was conducted, in which the K_{ow} of ponesimod was determined to be 4.3, whereas its PEC_{sw} was calculated to be 0.00965 µg/L. Based on these two values, the applicant originally concluded that neither a phase II evaluation nor a PBT evaluation are required. However, the

determination of the K_{ow} was considered potentially erroneous, and the calculation of the original PEC_{sw} was not supported. Considering this, the applicant was originally expected to clarify the experimental determination of the K_{ow} of ponesimod and conduct a phase II ERA assessment of ponesimod (as the PEC_{sw} trigger value is surpassed when correctly calculated). Additionally, a Tier B fish accumulation study was originally demanded because of the high lipophilicity of ponesimod. The applicant agreed upon these recommendations and committed himself to conduct the required ERA studies and submit them as post-authorisation measure in Q4 2022. This approach is endorsed.

2.3.7. Conclusion on the non-clinical aspects

A comprehensive study package covering PD, PK and toxicology has been submitted in support of the MAA of ACT-128800 (ponesimod). No major objections have been raised for the non-clinical part of the dossier. A number of other concerns were satisfactorily addressed, the submitted non-clinical programme therefore supports MA. However, note that the applicant committed himself to submit missing ERA studies as PAM [REC] in Q4 2022.

The CHMP considers the following measures necessary to address the non-clinical issues:

Description of post-authorisation measure(s)	
Updated Environmental Risk Assessment with required accompanying studies	Q4 2022

2.4. Clinical aspects

2.4.1. Introduction

The PK, PD, efficacy and safety of ponesimod were evaluated in 16 Phase 1, 1 Phase 2a (A2000), 1 Phase 2b (B201), and 1 Phase 3 (B301) clinical studies (Table 3). The 16 Phase 1 studies were performed in healthy subjects, or subjects otherwise healthy but with hepatic or renal impairment.

Overall, single oral doses of ponesimod ranged from 1 to 75 mg, and multiple oral doses ranged from 5 to 100 mg/day in healthy subjects for up to 22 days. Repeated doses of 10 to 40 mg were administered in subjects with MS.

In addition, a population pharmacokinetic (popPK) model was developed for ponesimod based on plasma concentration data of ponesimod obtained from 13 clinical studies. This popPK model was used to estimate metrics of systemic exposure for establishing exposure-response (ER) (PKPD) relationships.

Further, the applicant carried out a broad panel of *in vitro* studies to identify the enzymes involved in the ponesimod metabolism and to investigate potential enzyme induction and inhibition as well as transporter inhibition by ponesimod (Table 4).

GCP

The clinical trials were performed in accordance with GCP (Good Clinical Practice) 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.

- Tabular overview of clinical studies

Table 3: Summary of the clinical studies conducted to support the application of ponesimod

Type of Study	Study ID	Population	Number of Subjects Randomised	Dose/Formulation
AME	AC-058-106	Healthy subjects	6	Ponesimod 40 mg (single-dose), capsule
Single-dose PK	AC-058-101	Healthy subjects	48	Ponesimod 1, 3, 8, 20, 50, 75 mg (single-dose), capsule
	AC-058-114	Healthy subjects	17	Pilot phase: 5 mg, intravenous infusion over 3 h; Main phase: Treatment A: 5 mg, intravenous infusion over 3 h; Treatment B: 10 mg, tablet
Multiple-dose PK	AC-058-102	Healthy subjects	47	Part A: Ponesimod 5, 10, 20 mg qd, capsule Part B: Up-titration, ponesimod 10, 20, 40 mg qd, capsule
	AC-058-105	Healthy subjects	30	Up-titration Treatment A: ponesimod 2.5 mg bid, 5 mg bid, 20 mg qd, tablet Up-titration Treatment B: ponesimod 5 mg bid, 10 mg qd, 20 mg qd, tablet Up-titration Treatment C: ponesimod 10 mg qd, 20 mg qd, tablet
	AC-058-109	Healthy subjects	16	Up-titration, ponesimod 10, 20, 40, 60, 80, 100 mg qd, tablet
	AC-058-110	Healthy subjects	116	Group A: Up-titration, ponesimod 10, 20, 40, 60, 80, 100 mg qd, tablet Group B: Moxifloxacin 400 mg (single-dose), tablet
	AC-058-115	Healthy subjects	32	Regimen A: Up-titration, ponesimod 2, 3, 4, 5, 6, 7, 8, 9, 10, 20 mg qd, tablet Regimen B: Up-titration, ponesimod 10, 20 mg qd, tablet
	AC-058B201	Subjects with relapsing-remitting MS	464[a]	Group 1: Placebo Group 2: Ponesimod 10 mg qd, capsule Group 3: Up-titration, ponesimod 10, 20 mg qd, capsule Group 4: Up-titration, ponesimod 10, 20, 40 mg qd, capsule
	AC-058B301	Subjects with relapsing forms of MS	1133[b]	Up-titration period: Ponesimod 2, 3, 4, 5, 6, 7, 8, 9, 10, and 20 mg qd, tablet, or teriflunomide 14 mg qd, capsule. Maintenance period: Ponesimod 20 mg qd, capsule or teriflunomide 14 mg qd, capsule
	AC-058A200 **	Subjects with moderate to severe chronic plaque psoriasis.	66	Ponesimod or placebo multiple dose, irrespective of food intake: - Titration period: 10 mg qd for 4 days - Maintenance period: 20 mg qd
Bioequivalence	AC-058-103	Healthy subjects	12	Ponesimod 4x5mg capsules polymorphic Form A vs Ponesimod 1x20mg capsule polymorphic form C
	AC-058-108	Healthy subjects	14	Ponesimod 40 mg tablet vs 40mg capsule
Intrinsic factors	AC-058-112	Subjects with mild, moderate, or severe	32	Ponesimod 10 mg (single-dose), tablet

		hepatic impairment, and healthy subjects		
	AC-058-113	Subjects with moderate or severe renal function impairment, and healthy subjects	24	Ponesimod 10 mg (single-dose), tablet
	AC-058-107	Healthy subjects, Caucasians and Japanese	20	Ponesimod 40 mg (single-dose), capsule
Drug-drug interaction	AC-058-111*	Healthy subjects	23	Part A: Atenolol 50 mg qd, tablet Ponesimod 10 mg (single-dose), tablet Part B: Diltiazem, 240 mg qd, tablet Ponesimod 10 mg (single-dose), tablet
	AC-058-104	Healthy subjects	24	Treatment A: Ortho-Novum 1/35 (single-dose), tablet Ponesimod 10 , 20 , 40 mg qd, capsule Treatment B: Ortho-Novum 1/35 (single-dose), tablet Up-titration, ponesimod 10, 20, 40 mg qd, capsule
	AC-058-117	Healthy subjects	47[c]	Up-titration regimen of ponesimod 2, 3, 4, 5, 6, 7, 8, 9, 10, 20 mg qd, tablet Propranolol 80 mg qd, capsule

*study terminated prematurely due to safety reasons
**included in pop PK analysis
a 462 subjects treated
b 1131 subjects treated
c 52 subjects entered Period 1 and were treated with ponesimod, and 47 subjects were randomised to Period 2

Table 4: In vitro interaction studies

In vitro study	Objective
Metabolism	
B-16.027	Identification of the individual biochemical reactions involved in the formation of ponesimod metabolites, M12 and M13
B-18.004	Identification of human enzymes involved in ponesimod metabolism
FK13520	Identification of human enzymes involved in ponesimod metabolism
B-05.108	Identification of the number and proportions of the in vitro metabolites
Metabolism-mediated drug interactions	
B-05.078	Potential of ponesimod to inhibit CYP enzymes
B-13.080	Potential of ponesimod and its metabolite M13 to inhibit CYP and UGT enzymes
FK13543	Potential of ponesimod and its metabolite M13 to inhibit CYP2J2 and CYP3A4
B-08.581	Time dependent inhibition of CYP3A4 and 2C9 by Ponesimod
FK13536	Time-dependent inhibition of ponesimod and M13 on CYP enzymes
B-08.466	Potential of ponesimod on human to induce CYP
B-17.003	Potential of ponesimod and its metabolite M13 to induce CYP
FK13519	Potential of ponesimod and M13 to induce CYP3A4 messenger ribonucleic acid and in cultured human hepatocytes
Transporter mediated drug interactions	
FK13542	ponesimod and M13 as transporter substrates of BCRP
FK13541	ponesimod and M13 as transporter substrates of OATP1B1- and OATP1B3
FK13541	Potential of ponesimod and its metabolite M13 to inhibit uptake transporters OATP1B1, OATP1B3, OAT1, OAT3, OCT1 and OCT2 and efflux transporters MATE1, MATE2K, P-gp and BCRP

2.4.2. Pharmacokinetics

Bioanalytical methodology

LC-MS/MS methods were developed and validated for quantitation of ponesimod (parent compound) and metabolites in human plasma and human urine. In addition, two qualified methods were used for the determination of radiolabelled ponesimod and metabolites in human plasma, whole blood, human faeces and human urine. Further, the potential *in vivo* chiral inversion of ponesimod into ACT-128818 (S-enantiomer of ponesimod) was evaluated, and the potential for isomerisation has been investigated. A minor amount of S-enantiomer ACT-128818 is formed, between 0.96 and 1.62% of the amount of ponesimod. Therefore, achiral methods can be used to determine ponesimod. Exposure to ambient light might cause Z-E isomerisation, and therefore, in most studies, samples were protected from light.

It should be noted that the methods evolved in accordance with the requests from the former Food and Drug Administration (FDA) Guidance for Industry (2001) and its subsequent updates, and later the EMA Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**) was followed. In general, the inter- and intra-assay precision and accuracy for all assays of ponesimod in human plasma were within the acceptance criteria for the chosen quality control (QC) samples. Incurred sample reanalysis analyses have been applied for the major part of the studies, and the results were within the acceptance criteria recommended by EMA guideline.

Descriptive statistics have been presented for all PK studies. Pair-wise comparisons between 2 treatments for C_{max} and AUC values were based on log-transformed and dose-normalised data. Ratios and 90% confidence intervals (CIs) represent the ratio of point estimates of the geometric means and associated CIs.

Two popPK models have been developed and described by the applicant. The initial model only included data from phase I and II studies, the updated model also included data of the phase III study.

The PK of ponesimod was characterised using an open, 2-compartment disposition model with zero-order plus first-order absorption and linear elimination. The parameters were, in general, estimated with adequate precision. The popPK model was used to describe the PopPK characteristics of ponesimod including between-subject variability and to investigate the relationship between covariates (different formulations, demographic variables, the presence of food and the influence of disease). Goodness of fit plots were presented to visualise the influence and relevance of identified covariates. Plasma concentration data of ponesimod was obtained from 13 clinical studies. Rich plasma sampling was used in Phase I studies:AC-058-101, AC-058-102, AC-058-103, AC-058-105, AC-058-107, AC-058-108, AC-058-109, AC-058-110, AC-058-112, AC-058-113, AC-058-115. Sparse plasma sampling was used in studies AC-058A200 (study with psoriasis), and AC-058B201. The gathered data was pooled for the popPK analysis using non-linear mixed effect modelling approach.

An external model evaluation was performed using plasma concentrations from study AC-058b-301 (phase 3 trial) to verify the predictive performance of the proposed PopPK model. A maximum a posteriori assessment was used to estimate the PK model parameters and describe the available ponesimod plasma concentrations. When data from phase 3 study was applied, goodness of fit plots indicated a significant bias in the lower levels of dose. According to the applicant, that may be explained by the sparse sampling used in the B301 study and/or interstudy differences.

As a result, the B301 data were pooled together with the data from the previous Phase 1 and Phase 2 studies in order to obtain a global description of ponesimod PK that could improve the description of the sparse data from the B301 study. This data was pooled with the previously obtained Phase I and Phase II data. After the data was pooled, fixed and random effect were re-estimated. A summary of the key *post hoc* PK parameters is provided for all subjects included the PK dataset.

For the 2 mg dose data, the model still indicated some underprediction, despite a factor accounting for this dose level for the B301 data was included in the final model. The reason for this bias is unclear, and it was also in the reference PopPK model for the dose levels lower than 10 mg.

Absorption

After a single oral dose (10 mg) administration of ponesimod to healthy male subjects, the absolute oral bioavailability of ponesimod was 84%, and t_{max} was 4 h (study AC-058-114). There was no indication for a clinically relevant deviation from a dose-proportional PK. For the most important metabolites, M12 and M13, t_{max} was 4 h and 24 h respectively.

In the clinical phase 3 study AC-058B301 with the to-be-marketed formulation (20 mg tablets), food status did not affect the C_{max} at steady state. Also, in the popPK study, only a limited increase in bioavailability (7%) of fed compared to fasted status was observed. The limited increase is not considered to be clinically relevant; therefore, ponesimod can be administered with or without food.

In study AC-058-108, the rate of absorption was slightly higher after administration of the tablet compared to the capsule formulation, with a geometric mean ratio of C_{max} (Tablets/capsules) of 1.27 (90% CI 1.15-1.40). However, the exposure was comparable between the formulations, with a geometric mean ratio for AUC_{inf} of 1.07 (90% CI 0.95-1.19). As ponesimod is intended for chronic use and has a $t_{1/2}$ of more than 24 hours, the AUC is considered the most relevant PK parameter. Since no clinical significance of these findings is anticipated, no further inquiries are made for this procedure.

Distribution

The apparent volume of distribution (Vd) in healthy subjects was 160 L (study AC-058-114). In the popPK analysis, the predicted Vd of the central compartment in healthy subjects was 165 L, whereas in subjects with MS, it was 200 L. The predicted Vd of the peripheral compartment was 107 L in white subjects and 67 L in black subjects. The Vd indicates extensive distribution to the tissues. *In vitro* mean plasma protein binding of ponesimod was 99.6% (investigated concentration range was 100 to 200,000 ng/mL). Ponesimod was found to bind to both human serum albumin (99% bound) and alpha-1-acid glycoprotein (94-96% bound). The *in vitro* mean protein binding of M13 was 99.0%. No concentration-dependent effects were observed in the concentration range 100 to 20,000 ng/mL. In subjects with renal impairment, plasma protein binding was 97.8 – 99.5%. In subjects with hepatic impairment, plasma protein binding was 99.1- 99.5%. Blood/plasma ratio was 0.68 for ponesimod and 0.50 for M13. There was no evidence for entero-hepatic circulation.

Since the protein binding has been >99% in some studies, the applicant was invited to justify why no displacement studies were performed. The applicant's justification is that ponesimod concentrations are low, it is restrictively eliminated, and no correlations were revealed in patients with impaired hepatic function. The justification is deemed acceptable.

Ponesimod is a neutral, lipophilic molecule that passively permeates across cell membranes and is not a substrate of the active transporters P-gp, BCRP, OATP1B1, or OATP1B3. The applicant has not evaluated whether ponesimod is a substrate for uptake transporters (OAT1, OAT3, OCT1, and OCT2) or efflux transporters (MATE1, and MATE2K). Upon request, the applicant explained that the potential for ponesimod to be a substrate of predominantly renal transporters (such as OAT1, OAT3, MATE1, MATE2K and OCT2) was not considered relevant, and therefore was not evaluated. It is agreed that no active renal transport of ponesimod is expected as it not excreted renally. As uptake transporters OAT1 and OAT3, and efflux transporter MATE2K are primarily expressed in the kidney, it is acceptable that these transporters are not evaluated. However, uptake transporter OCT1 is primarily expressed in the liver and uptake transporter OCT3 and efflux transporter MATE1 are both expressed in kidney and liver. The applicant was asked to evaluate if active transport by these transporters is relevant for ponesimod, or to justify the lack of in vitro studies. Upon request, the applicant adequately justified that no clinically relevant transporter interactions for ponesimod are expected. No clinically relevant interaction with the liver transporters is expected based on limited amount of unchanged drug eliminated via hepatic secretion, the good passive cell permeability of ponesimod and non-clinical study results that indicate the lack of involvement of active transport into the hepatocytes.

Elimination

After a single oral dose, $t_{1/2}$ of ponesimod ranged 21.7–33.4 h. For the metabolites M12 and M13, $t_{1/2}$ ranged 31.7-47.9 h for M12 and 36.0–45.7 h for M13. In multiple-dose studies, $t_{1/2}$ of ponesimod ranged 30.9–33.5 h. In the popPK, the $t_{1/2}$ of ponesimod was also estimated as 33 h.

Clearance was 3.8 L/h in healthy subjects after a single intravenous infusion. In the popPK, clearance was shown to be dependent on the hepatic impairment status, i.e. it was estimated as 6.64 L/h in healthy subjects, and 4.66 L/h, 3.18 L/h and 2.13 L/h in mild, moderate and severe hepatic impaired subjects.

After a single oral administration of 14C-ponesimod to healthy male subjects, 57-80% was recovered in faeces, 10-18% in urine and 0.6-1.9% in expired air. Ponesimod accounted for 16% of the dose in faeces, which may well represent the non-absorbed part, since absolute oral bioavailability was found to be 84%. Unchanged ponesimod was not found in urine. In faeces, besides unchanged ponesimod, metabolite M12 was the major component (22% of the radioactivity in faeces). Other metabolites

represented <1-5% of the radioactivity in faeces. In urine, only small metabolites were found (<1–7% of the radioactivity in urine).

The mean cumulative recovery of radioactivity in urine and faeces was 77.9%, which is below the preferable level of 90% as indicated in the guideline CPMP/EWP/560/95/Rev.1. Upon request, the applicant clarified that the level of radioactivity recovered (77.9%) is associated with a long terminal $t_{1/2}$ of radioactivity in plasma and slow elimination of radioactivity.

In plasma, unchanged ponesimod was the major component, representing approximately 66-77% of drug-related exposure. The most important metabolites in plasma were M12 and M13, representing approximately 6-8% and 17-26% of drug-related exposure, across studies (multiple dose study AC-058-109 and AC-058-110 and single-dose studies AC058112, AC058113, AC058114, AC058108). However, the mass balance study AC-058-106 suggests that the contribution of metabolite M12 accounted for more than 10% of the total radioactive dose administered when the fraction excreted in faeces is taken into account. Based on the proposed metabolic pathway in humans, M12 pathway accounted for approximately 19% of the total radioactive dose. M12 is formed by oxidation and M13 by truncation of the ethylene glycol side chain by 1 carbon and oxidation. Based on nonclinical studies, the formation of M12 involves multiple CYPs (2J2, 3A4, 3A5, 4F3A, and 4F12) and non-CYP enzymes. Ponesimod also undergoes direct glucuronidation (mainly UGT1A1 and UGT2B7). CYP2J2 appears to be the main enzyme responsible for the formation of M12. In addition, several minor metabolites were identified in human plasma samples (M6, M8, M9, M10, M11, and M15). None of the metabolites is pharmacologically active. In the AC-058-106 study, the applicant states that 11 metabolites in the urine and one metabolite in the faeces are unidentified. The remaining unidentified fraction of the radioactivity are small peaks and are not identifiable.

According to the applicant, data from plasma pools indicate that AUC_{inf} of ponesimod corresponds to 66.1% of total drug-related radioactive exposure. However, median AUC_{inf} of ponesimod from pooled plasma samples is only 2,668 ng-eq*h/mL, whereas the median AUC_{inf} of total plasma radioactivity is 8954 ng-eq*h/mL. Furthermore, the median AUC_{inf} of ponesimod obtained from plasma PK sampling is 3930 ng·h/mL, which corresponds to approximately 44% of the AUC_{inf} of total radioactivity in plasma. No additional radioactivity spikes, besides M12, M13 and Ponesimod, were registered.

After administration of ponesimod (being in R-configuration), only a minor amount of S-enantiomer ACT-128818 is formed, i.e., between 0.96 and 1.62% of the amount of ponesimod. This low amount has no impact on the conclusions from the PK and E-R analysis of ponesimod, and therefore, there is no need to use a chiral method for the analysis of ponesimod

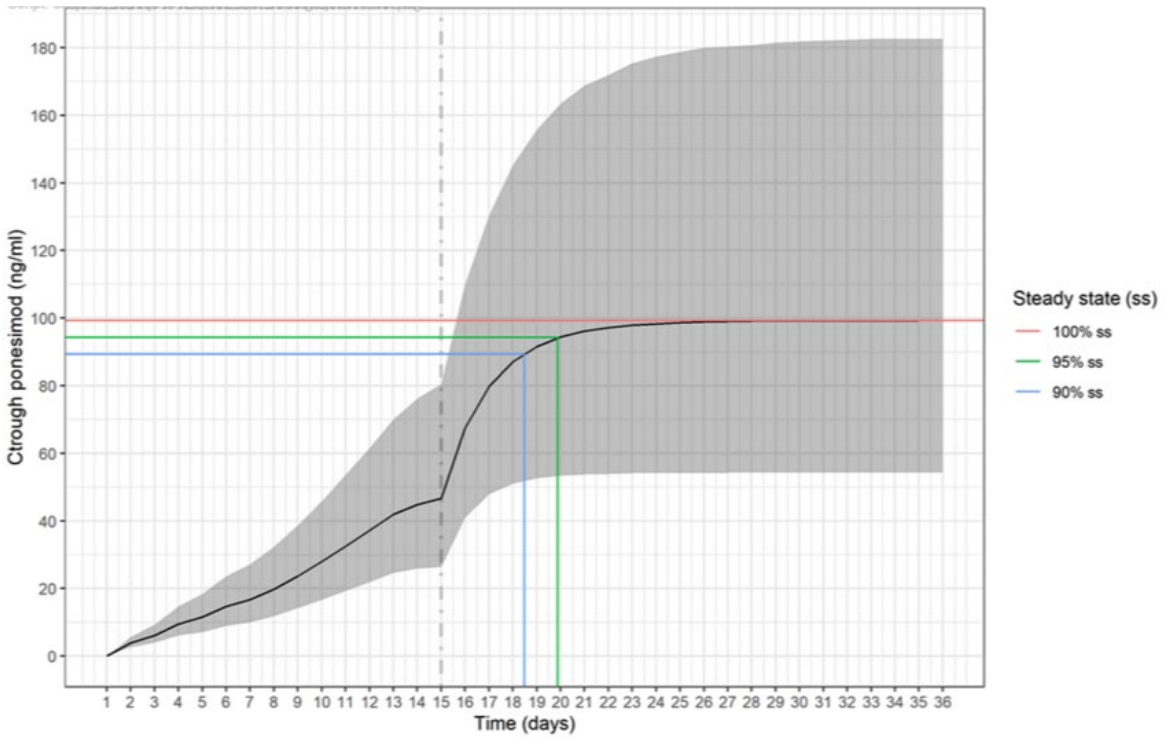
Dose proportionality and time dependencies

After single-dose administration to healthy subjects, C_{max} and AUC_{inf} of ponesimod increased approximately dose-proportionally across a dose range of 1 – 75 mg. After multiple-dose administration to healthy subjects, slight variation in outcome was observed; however, no indication for a clinically relevant deviation from dose-proportional PK was observed. In the Phase 2 study in subjects with MS, plasma concentrations ponesimod increased approximately dose-proportionally from 10 to 40 mg/day. The linear compartmental model in the popPK analysis described the data sufficiently well, indicating that there is no reason to assume that there is a relevant deviation from dose-proportionality in the PK.

In a multiple-dose study AC-058-102 in healthy subjects, a steady-state was achieved in approximately 6 days. In the absence of data on achievement of steady-state after up-titration, the original popPK

model described by Lott 2017[1] was used to simulate the trough plasma concentration(C_{trough}) during the up-titration period and the subsequent multiple administration of the 20 mg QD maintenance dose (Figure 3). Based on these simulations, it is concluded that 90% of steady-state is achieved after administration of 4 doses of the maintenance dose (day 18 from the start of the up-titration), while 95% of steady-state is reached after 5 doses of the maintenance dose (day 19).

Figure 3: Ctrough during the up-titration and subsequent multiple administration of 20mg dose



The grey dot-dashed vertical line indicates the time of the first 20mg dose. The solid black line represents the median and the grey area represents the 90th prediction interval (i.e. 5th and 95th percentiles of simulated data) of 5000 stochastic simulations. The blue, green and red horizontal lines indicate 90%, 95% and 100% of steady state Ctrough, respectively; the corresponding blue and green vertical lines indicating the corresponding time of achievement after the start of the up-titration regimen.

In a study in patients with RRMS, no relevant accumulation was observed from 168 hours post-administration onwards to week 24 following administration of 10–40 mg/day.

Intra- and inter-individual variability

Low to moderate inter-subject variability was observed in healthy subjects, with coefficient of variation (CV) ranging 6 – 33% for ponesimod, 21 – 38% for M12 and 21 – 43% for M13. In line with this, in the popPK study D-16.437, patients were included, and estimated inter-subject variability was low to moderate (10 – 28%) regarding the apparent central and peripheral Vd, the apparent inter-compartmental clearance and clearance. It was higher (41–57%) regarding the absorption-related parameters.

[1] Lott D, Lehr T, Dingemanse J, Krause A. Impact of Demographics, Organ Impairment, Disease, Formulation, and Food on the Pharmacokinetics of the Selective S1P1 Receptor Modulator Ponesimod Based on 13 Clinical Studies. Clin Pharmacokinet. 2017; 56: 395–408.

Upon request, the applicant clarified that intra-subject variability could only be evaluated from 2 studies (n=12 for each formulation in AC-058-103 and n=14 each for AC-058-108). Based on the presented data the intra-subject variability is estimated to be low, between 12-20%.

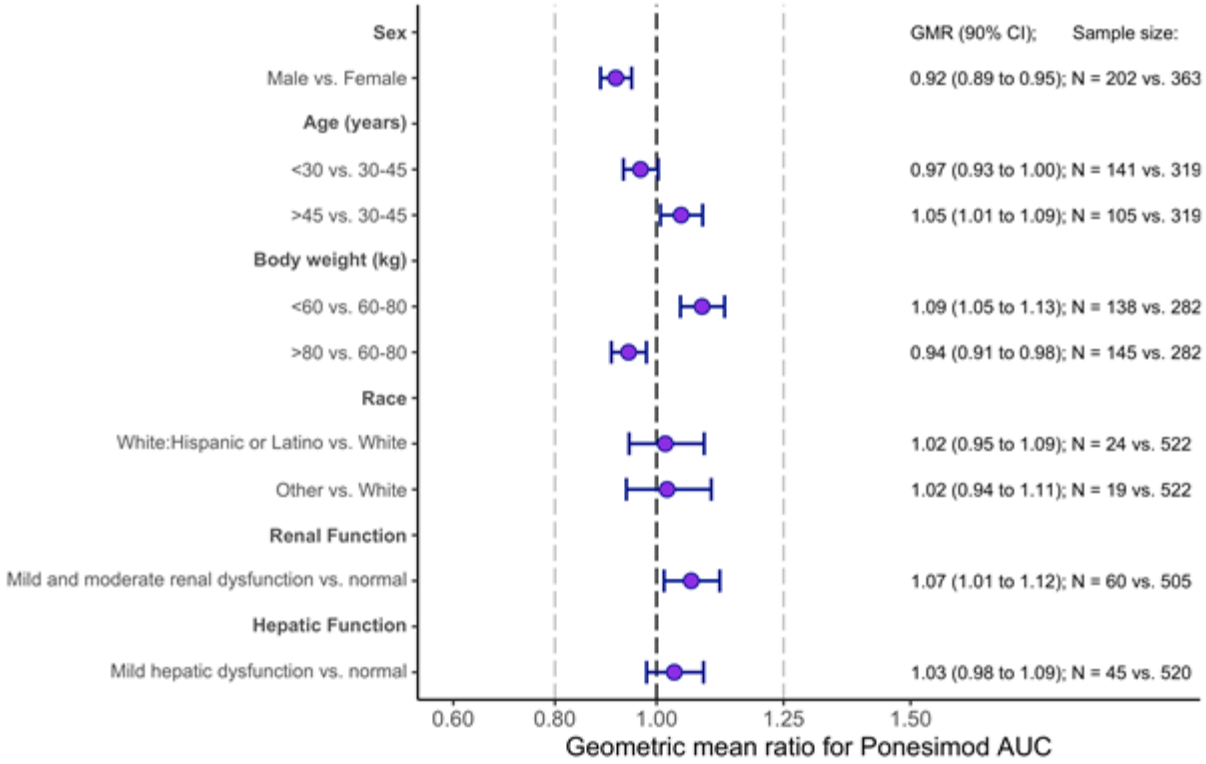
Target population

Based on interstudy comparisons, C_{trough} values in patients at 20 mg/day were comparable to the values in healthy subjects. This was confirmed in the popPK analysis, where no clinically relevant effect of MS on the PK of ponesimod was found. In the population, PK study subjects with MS had a slight decrease in C_{max} at steady state of 5% but $C_{trough,ss}$ were 4% higher in subjects with MS.

Special populations

Special population single-dose clinical pharmacology trials were performed in subjects with renal (AC-058-113) or hepatic impairment (AC-058-112). The influence of race (Japanese vs. Caucasian) has been evaluated in study (AC-058-107). The influence of other covariates on exposure has been evaluated using a popPK analysis. Covariates included in this analysis were: sex, age race, ethnicity, BW, renal function, and hepatic impairment.

Figure 4: Forest Plot for the Covariate Evaluation Effect Over the Ponesimod Systemic Exposure in MS Subjects



AUC=area under concentration-time curve at the steady-state; GMR=geometric mean ratio; MS=multiple sclerosis

Renal impairment

Ponesimod exposure did not significantly increase with the severity of renal impairment. Based on the results of study AC-058-113, no dose adjustments are needed in patients with mild to severe renal impairment. These results are in line with the results of the mass balance study, in which was shown that renal elimination is a minor pathway. About 10-18% of the radioactivity was excreted in the urine. In the popPK study, renal impairment had no effect on the PK of ponesimod.

Hepatic impairment

Ponesimod is extensively metabolised in the liver, and the PK of ponesimod and its metabolites are affected by hepatic impairment. In phase I Study AC-058-112, the AUC and $t_{1/2}$ of ponesimod and its metabolites were increased in subjects with hepatic impairment compared with healthy subjects. Hepatically impaired subjects of Child-Pugh class A showed a 1.3-fold (90% CI: 1.0-1.8), of Child-Pugh class B a 2.0-fold (1.5-2.7), and of Child-Pugh class C a 3.1-fold (2.2-4.3) increase in total ponesimod exposure (AUC_{inf}) compared with healthy subjects. The respective geometric mean ratio of elimination $t_{1/2}$ were 1.5 (90% CI: 1.2 1.8), 1.8 (1.3-2.5), and 2.6 (2.0-3.3), indicating reduced clearance of ponesimod.

The effect of hepatic impairment was also assessed using popPK modelling. A pooled data set was compiled using the data of phase I/II/ III Studies, with a total number of subjects of 1245 subjects, including 63 patients with mild hepatic impairment. Different classifications were used to identify the hepatic impairment patients (Child-Pugh classification was used in the phase I study, and NCI-ODWG criteria were used in phase II and III studies). In patients with a mild hepatic impairment, the exposure (AUC) of ponesimod was increased by 12%. Limited clinical data are available on patients with class B (moderate) hepatic insufficiency. Only four patients with moderate hepatic impairment were included in the phase III study, and eight subjects received a single dose of ponesimod in the phase I study AC-058-112. In these patients the exposure (AUC) of ponesimod was increased by 44%, however, these data should be interpreted with caution as only a limited number of clinical data are available on patients with moderate hepatic insufficiency.

The effect of a mild hepatic impairment is 10-30%, slightly above normal subject variability. This is not expected to be clinically relevant so it can be agreed that no dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh class A) as stated in section 4.2 of the SmPC. Section 4.3 of the SmPC also states that ponesimod is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh class B and C, respectively).

Gender

No relevant gender effect was found for ponesimod. For the metabolites, M12 and M13, slightly higher C_{max} and AUC_{0-24} values were observed for females compared to males in one of two studies in healthy subjects. This is not considered clinically relevant, since M12 and M13 are not pharmacologically active.

Race

In a phase 1 study, the exposure to ponesimod (AUC_{inf} and area under the concentration-time curve from time 0 to the last measurable concentration [AUC_{0-t}]) after single-dose oral administration of 40 mg ponesimod was about 15% higher in Japanese subjects compared with Caucasian subjects. Further, in the popPK analysis D-16.437, estimated area under the concentration-time curve during a dose interval (AUC_{τ}) was 18% higher in black subjects (N=4) compared to white subjects due to the estimated lower clearance and the lower peripheral volume of distribution. In all cases, the effect of race, however, was within the range of the inter-subject variability and therefore considered as not clinically relevant. Dose adjustments based on race are not necessary.

Body weight

No dedicated study has been conducted on the effect of BW on the PK of ponesimod. In the popPK analysis, the exposure was estimated to increase with lower BW and to decrease with higher BW (approximately 30% difference in AUC_T over the 5–95th percentile of BW). The effect of BW on AUC_T of ponesimod was considered not clinically relevant, with the change in exposure upon lower or higher BW than average being within the range of inter-subject variability (CV 14–33%). Also for very heavy patients (for instance with BW 150 kg), the exposure is still expected to be within the range of inter-subject variability. Dose adjustments based on BW are not necessary.

Age

No specific study has been conducted on the effect of age on the PK of ponesimod. In the population, based on which the popPK analysis was performed, age (18-65 year) was not found to significantly influence the PK of ponesimod. No subjects older than 65 were included in the clinical studies. Upon request, the applicant was invited to update the SmPC as follows: section 4.2 "Clinical studies of ponesimod did not include patients aged 65 years and older. Ponesimod should be prescribed with caution in patients aged 65 years and over due to the lack of data on safety and efficacy" and section 5.2 "ponesimod has not been investigated in the elderly population (>65 years)". Age was not a covariate in the popPK model, and patients over 55 years old were in general not included in the studies with ponesimod. However, due to the fact that the number of late-onset MS cases is increasing, and overall, the age of patients with MS will increase over time with the new treatment options, the applicant will be inquired further regarding this in the Safety part. Safety in the elderly is indicated as missing information in the RMP and will be followed post-marketing.

Currently, there are no data in paediatric patients. A study in paediatric patients aged 10–18 years is planned. In the SmPC, it is stated that the safety and efficacy in children aged less than 18 years has not been established and that ponesimod is indicated in adult patients only. This is agreed.

Interaction studies

The interaction potential of ponesimod and its inactive metabolite M13 was investigated using *in vitro* tests. Although M12 is the most abundant metabolite in excreta, it has not been investigated in the *in vitro* interaction studies as the concentration of M12 is <10% of the total amount present in plasma.

Based on *in vitro* tests it can be concluded that ponesimod is extensively metabolised and several different enzymes are involved in the metabolism of ponesimod. Therefore, it is expected that the PK of ponesimod will not be affected by most inhibitors of metabolizing enzymes. The *in vitro* inhibition findings do not indicate a potential for clinically relevant inhibition risk for any of the CYPs or UGTs evaluated. Coadministration of strong inducers of multiple metabolic pathways may decrease the systemic exposure of ponesimod. It is unclear whether this decrease is clinically relevant.

The company conducted three clinical DDI studies and two physiologically based pharmacokinetic simulations to identify possible interactions with CYP450 enzymes. In DDI study AC-058-104 no PK interaction was observed with the hormonal contraceptive of Ortho-Novum (containing 1 mg norethisterone/norethindrone and 35 µg ethinyl estradiol). DDI studies AC-058-111 (with atenolol and diltiazem) and AC-058-117 (with propranolol) were mainly designed to investigate cardiac safety. The effects on HR and rhythm were measured as the primary endpoint in these studies, and the effects on the PK were analysed as a secondary objective. No significant changes in the PK of ponesimod or propranolol were observed in study AC-058-117. Study 058-111 was prematurely terminated due to safety reasons. The PK of ponesimod, atenolol or diltiazem does not appear to be affected; however, it should be noted that the data are difficult to interpret due to very limited PK data available from this

study. Further, based on the PBPK simulations FK13357 and FK13637 no clinically significant interactions are expected between ponesimod and substrates of CYP2C9, CYP2C19 and CYP3A4/5.

Ponesimod displays pH-dependent dissolution. The applicant has not investigated nor discussed the potential for interaction with drugs that increase gastric pH and may affect the dissolution of the ponesimod *in vivo*. Upon request, the applicant clarified that although ponesimod displays pH-dependent dissolution, the potential DDI risk of ponesimod with pH modulators is considered to be low. Ponesimod is a Biopharmaceutical Classification System class 2 drug, with low solubility over the physiological pH range, with absorption being driven by permeability, rather than solubility. This is supported by the limited effect of food on the PK of ponesimod. An analysis on the effect of antacids, using data collected in clinical studies B201 and B301 showed that steady-state concentrations of ponesimod were similar between subjects who received an antacid and subjects without antacid. Based on this no DDI study with a drug that increases gastric pH is required.

2.4.3. Pharmacodynamics

The applicant has not performed any dedicated pharmacology studies. Four PK studies, AC-058-105, AC-058-110, AC-058-115 and AC-058-117 provided PD data on cardiac effects.

Further PD data and PK/PD data is available from the Phase 2 dose-finding study AC-058B201 and the pivotal Phase 3 study AC-058B301.

Three popPK/PD analyses were performed to investigate effects on peripheral lymphocytes counts, HR and QTc. E-R modelling based on data from the dose-response study and pivotal Phase 3 study was performed as well.

Mechanism of action

Ponesimod is a S1P modulator, with high affinity to $S1P_1$ and selectivity for this receptor over other S1P. Ponesimod leads to internalisation of the $S1P_1$ where it is degraded by the intracellular proteasomal system. As a consequence, lymphocytes are deprived of the necessary signal to egress from lymphoid organs, leading to a reduction of circulating lymphocytes. T and B cells are most sensitive to ponesimod-mediated sequestration. In contrast, monocyte, natural killer (NK) cell, and neutrophil counts are not reduced by ponesimod.

Primary and Secondary pharmacology

Ponesimod effect on peripheral lymphocytes counts

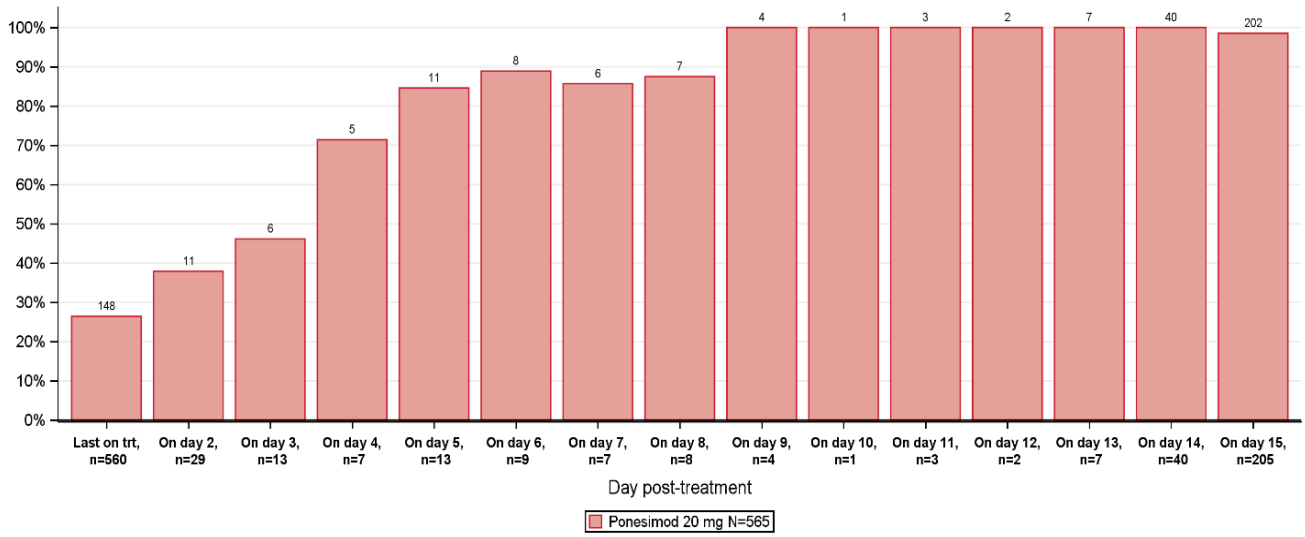
Ponesimod induced a dose-related decrease in lymphocytes levels in the blood. No further decreases in lymphocyte counts were observed at doses>60 mg/day. The maximal reduction in total lymphocytes observed after a dose of 20 mg/day was 74%, and the reduction observed at C_{trough} was 59%. The decrease in lymphocytes was reversible after 3–10 days. Effects on T-helper cells, cytotoxic T cells and regulatory T cells and on B cells were generally comparable to the effect on total lymphocytes. No relevant decrease in NK cells was observed (compared to placebo). The effect on cytotoxic T cells was slightly less than on T-helper cells and B cells.

The PK/PD of the effect of ponesimod on lymphocytes levels was characterised based on data in healthy subjects, using an indirect-response model, which was based on the popPK model, supplemented with the appearance of lymphocytes in blood following a zero-order process and disappearance from blood according to a first-order process. In general, parameters were estimated with adequate precision,

except for effect on NK cells, which can be explained by the lack of a clear effect on NK cells. The applicant clarified that a limited number of outliers was excluded from the analysis. The exclusions were due to conditional weighted residuals being > 6. This was in accordance with the analysis plan. A decrease in the baseline of lymphocytes was predicted with increasing age, but no effect of age on the relative change from baseline was predicted. The effects of sex and BW on the model were predicted to be negligible. Maximum predicted reduction in total lymphocytes was 87%. Simulating dosing scenarios with the PK/PD model showed that only a further reduction of 8% was observed when increasing the dose from 20 to 40 mg. When the dose was increased from 40 mg to 100 mg, a further reduction of 4–6% was observed. The predicted effect on cytotoxic T cells was slightly less than on T-helper cells and B cells, as was found in the studies. The PK/PD model was successfully applied to the data from studies AC-058B201 and AC-058B301, indicating that no differences are to be expected in the ponesimod effect on total lymphocyte counts between healthy subjects and subjects with MS.

In both clinical studies in patients with RMS (B201 and B301), a rapid decline in peripheral lymphocyte counts was observed, which remained thereafter stable until treatment withdrawal. Upon request, the applicant clarified that the percentage of subjects with lymphocyte counts above $0.8x10^9$/L was 37.9% (11/29), 84.6% (11/13) and 98.5% (202/205) in study B301, by FU Day 2, FU day 5 and FU day 15, respectively (Figure 5). Similar results were seen in study B201. This indicates that lymphocyte count indeed returns to normal for the majority of subjects within 2 weeks.

Figure 5: B301: Number and Percent of Subjects With Peripheral Blood Lymphocyte Counts ≥0.8 * 109/L, by Post-Treatment Day



Only central laboratory results (scheduled and unscheduled) are included. Last on treatment: latest treatment-emergent assessment prior to or on the day after last study drug intake. n consists of subjects with post-treatment lymphocyte count available on each post treatment timepoint.

In the dose-response study B201, the reduction in lymphocyte counts generally needed for therapeutic response, i.e. approximately 70%, was reached with the 20 mg and 40 mg doses. This supports omitting the 10 mg dose from further studies.

Ponesimod effect on heart rate

Ponesimod induces a transient, dose-dependent decrease in HR, which is more prominent on the first day of ponesimod dosing. The negative chronotropic effect disappears due to the $S1P_1$ receptor internalisation in cardiomyocytes induced by ponesimod initial doses resulting in tolerance.

Effect of up-titration regimen of ponesimod on HR and rhythm

Study AC-058-115 was conducted to investigate and optimise the ponesimod up-titration regimen. Two up-titration regimens were compared in a double-blind, placebo-controlled, randomised, 2-way crossover study in 32 healthy subjects (active: placebo ratio of 3:1). The gradual up-titration regimen with a starting dose of 2 mg later used in Studies B301/B303 was designated regimen A, and the regimen with a starting dose of 10 mg used in Studies B201/B202 was designated regimen B. The first dose of ponesimod (Day 2) resulted in a transient decrease in mean hourly HR from baseline. The decrease as assessed by Holter and 12-lead ECG was greater with treatment regimen B (maximum mean decrease: 12 bpm and 13 bpm, respectively) than with regimen A (6 bpm and 9 bpm, respectively) and placebo (0 bpm and 4 bpm, respectively). These maximum mean decreases occurred 2–3 h postdose and mean hourly HR had returned to predose values by 4–5 h postdose. No further postdose decrease in mean hourly HR was observed on Day 3 and later study days in either regimen. The proportion of subjects who experienced an AV block (defined as PR >210 ms) was 25% for all treatment groups. However, the total number of occurrences of any AV block was largest during regimen B (143) followed by regimen A (79) and placebo (33). The maximum observed PR intervals were 222 ms (Day –1, predose), 236 ms (Day 4, 3 h), and 220 ms (Day -1, 2 h) in regimen A, B, and placebo, respectively.

Modelling for ponesimod effect on HR and rhythm

A PK/PD model, including an HR baseline with circadian oscillation, the direct effect of ponesimod on HR decrease, and the development of tolerance during up-titration (modulated by ponesimod plasma concentrations), described the effect of ponesimod on HR and its variability observed in the data from 9 Phase 1 studies in healthy subjects.

Modelling indicated that after 1 week of treatment with ponesimod at 20 mg/day, the tolerance effect is almost fully (>90%) developed; this was consistent with observed predose HRs in subjects receiving ponesimod treatment being similar to the baseline (i.e., prior to any ponesimod dosing) values observed in the Phase 2b Study B201.

With the exception of baseline HR, no clinically relevant effects of other covariates (age, sex, race, and body size) on ponesimod effects on HR were identified in healthy subjects or subjects with MS.

With the gradual up-titration of ponesimod dose used in Study B301, no HR ≤40 bpm cases were observed in subjects with HR at baseline ≥55 bpm. This finding supports the recommendation of HR monitoring after the first ponesimod dose only in subjects with a baseline HR<55 bpm. The incidence of marked bradycardia (HR ≤40 bpm) after the first 2 mg dose was 0.53% (lower than that observed in Study B201 with the first dose of 10 mg, 0.89%) and no HR ≤40 bpm was observed in the subsequent days of up-titration.

Simulation results also indicated that after treatment discontinuation lasting up to 3 days either during up-titration or at maintenance dosing, ponesimod dosing could be resumed without the need of reinitiating the up-titration, while if treatment is discontinued for 4 or more days, ponesimod up-titration should be reinitiated from the starting dose of 2 mg to minimise the HR effects. This recommendation is valid for subjects with normal and mildly impaired hepatic.

Ponesimod effect on QT interval

In Study AC-058-110, after multiple-dose administration of ponesimod at supratherapeutic doses of 40 and 100 mg as tablets in healthy subjects, ponesimod caused QTc prolongation, with a mean peak effect on the placebo-corrected change from baseline in the individually corrected QT (ΔΔQTcI) of 6.9 ms on 40 mg ponesimod and 9.1 ms on 100 mg ponesimod. Graphical exploration of the data indicated a lack of delayed effects. The concentration-effect modelling confirmed the findings of a QT prolongation caused by ponesimod: the upper limits of the 2-sided 90% CI of the ΔΔQTcI were 6.73 and 9.52 at 40 mg and

100 mg, respectively. The extrapolation of the model results to the proposed therapeutic 20 mg dose of ponesimod, provided an upper limit of the 2-sided 90% CIs of 5.9 ms. In the Phase 3 study, B301, mean changes from baseline to Week 108 in QT corrected using Fridericia's formula (QTcF) ranged from 1.8 to 5.2 ms in the ponesimod 20 mg group.

Pulmonary effect of ponesimod

Ponesimod, administered at 20 mg daily dose in the Phase 3 Study B301, led to an exposure dependent reduction of forced expiratory volume in 1 second (FEV_1), mostly occurring in the first month after treatment initiation. The net (i.e., discounted of the effect of teriflunomide treatment) model-predicted effect led to a 5.5% decrease compared to baseline at the median AUC of 3,687 ng/mL. This net effect is consistent with the 5% reduction on FEV_1 observed in Study B201 at the same dose level. As expected, and also consistent with findings in B201, significant effects of sex, age, race, and baseline expanded disability status scale (EDSS) on FEV_1 at baseline were found, however, since none of these covariates was associated with the magnitude of ponesimod effect on FEV_1, dosage adjustments on the basis of these covariates is not warranted. In addition, there were significant effects of age and BW on the ponesimod effect, where the effect of ponesimod on FEV_1 increases with increasing BW and decreases with increasing age.

Exposure-response modelling

Study B201

E-R analysis of the cumulative sum of new gadolinium enhancing (Gd+) lesions between Week 12 and 24 as well as ARR was performed on data from the dose-response study B201. Graphical exploration and regression analysis were used to model the relationship between metrics of systemic exposure to ponesimod (AUC and lymphocyte decrease) and the efficacy and safety endpoints. The potential effect of baseline covariates (age, sex, BW, race, Gd+ lesions, and EDSS) was also explored.

The E-R modelling on data from the dose-response study B201 demonstrated a clear E-R relationship in terms of Gd+ lesions. The predicted decrease in cumulative new Gd+ lesions plateaus at around 5000 ng·h/mL, suggesting only a small additional benefit of doses higher than 20 mg QD.

The model predicted an additional decrease of approximately 10% in ARR with the 40 mg dose as compared to 20 mg could be considered substantial. However, based on the clear dose-response relationship in AE, this additional benefit is not considered such that would justify the 40 mg dose.

Study B301

E-R analysis of the CUAL and ARR was performed on data from the pivotal study B301. Graphical exploration and regression analysis for count data were used to characterise the relationship between ponesimod exposure and these endpoints, and the potential effect of baseline covariates (age, sex, BW, race, T1, EDSS and former use of DMT) was also explored.

The E-R modelling suggests a clear E-R in terms of CUALs within the exposure range observed for 20 mg maintenance dose of ponesimod. Based on indirect comparison, within the usual range of exposures of this dose, the E-R relationship in terms of ARR is rather flat.

2.4.4. Discussion on clinical pharmacology

In general, the bioanalytical methods used to determine the concentrations ponesimod and its metabolites M12 and M13 were acceptable. Although the middle QC sample (both validation and during

the analysis of study samples) does not comply with the recommendation in EMA guideline (30-50% of the upper limit of quantification [ULQC]), considering the actually found concentration level in trial samples the chosen middle QC lower than 50% of ULQC covers the obtained results in most of the studies and is more suitable. No question was raised regarding this aspect. In general, the inter- and intra-assay precision and accuracy for all assays of ponesimod in human plasma were within the acceptance criteria for the chosen QC samples. Incurred sample reanalysis analyses have been applied for the major part of the studies, and the results were within the acceptance criteria recommended by EMA guideline. Information on the potential influence of other drugs on the assay performance has been provided for none of the bioanalytical validation reports that have been used for the determination of ponesimod in plasma. The applicant has justified that based on the molecular weight no MS/MS interference is anticipated between concomitant medication and ponesimod, its internal standard and its main metabolites M12 and M13.

The PK of ponesimod have been studied adequately. Ponesimod is absorbed well after oral administration (84%) and is widely distributed into tissues. Ponesimod is excreted for the major part in faeces (57-80%) and for a minor part in urine (10-18%).

Estimated inter-subject variability was low to moderate (10–28%) regarding the apparent central and peripheral Vd, the apparent inter-compartmental clearance and clearance. It was higher (41–57%) regarding the absorption-related parameters. There were only a limited number of Phase 1 studies in which subjects received replicate doses of ponesimod; therefore, intra-subject variability could only be evaluated from 2 studies based on which, intra-subject variability is estimated to be low, between 12-20%.

The to be registered formulation is an immediate-release tablet. In the clinical studies, patients were instructed to swallow the tablets whole. The effect of chewing, crushing, or suspending the tablets was not evaluated in a formal study. Despite of this, patients with swallowing problems do not need to swallow the tablet whole, as no clinically significant crushing effects are expected from the Quality or PK point of view based on the composition of the products and the PK of different formulations observed during clinical development.

In clinical phase 3 study, the to-be-marketed tablets were overencapsulated. Overencapsulation can be accepted based on cross-study comparison. Cross-study comparisons indicate that ponesimod exposure from the overencapsulated tablet used in the Phase 3 study (AC-058B301) is consistent with the exposure in a Phase 1 study (AC-058-115) with the non-overencapsulated tablet.

About 10-20% of the administered dose is eliminated renally, and renal impairment did not affect the PK of ponesimod. Therefore, no dose adjustments are needed in patients with mild to severe renal impairment. The effect of dialysis on the PK of ponesimod has not been studied. Due to the high plasma-protein binding of ponesimod lack of effect in severe renal impairment, no dose-adjustment is anticipated in patients undergoing haemodialysis.

Ponesimod is extensively metabolised, and patients with hepatic impairment had a substantially increased exposure of ponesimod. After a single 10 mg oral dose of ponesimod, subjects with mild hepatic impairment (Child-Pugh class A) showed a 1.3-fold, moderate hepatic impairment (Child-Pugh class B) a 2.0 fold, and severe hepatic impairment (Child-Pugh class C) a 3.1-fold increase in total ponesimod exposure (AUCinf) compared to healthy subjects (Study AC-058-112).

The 10-30% increase of ponesimod exposure observed in patients with mild hepatic impairment (in Study AC-058-112 and population PK study) was not expected to be clinically relevant. However, upon request, the applicant provided an additional analysis of the data available on patients with mild hepatic impairment to support that ponesimod 20mg can be safely used in this subpopulation. A pooled data set was compiled using the data of phase 1/2/3 Studies, with a total number of subjects of 1,245 subjects

including 63 patients with mild hepatic impairment based on Child-Pugh Criteria (55 subjects classified based on the National Cancer Institute - Organ Dysfunction Working Group criteria). The exposure (AUC) of ponesimod increased by 12% in these patients. No dose adjustment is necessary for patients with mild hepatic impairment (Child-Pugh class A) as stated in section 4.2 of the SmPC. Standard monitoring of safety risks is expected to be sufficient for patients with mild hepatic impairment. SmPC section 4.4 clearly states that monitoring of several safety parameters is required, precautions include monitoring of liver function tests to detect worsening of hepatic dysfunction in an early stage. Limited clinical data are available on patients with class B (moderate) hepatic insufficiency. Only four patients were included in the phase 3 Study, and eight subjects received a single dose of ponesimod in the phase I study AC-058-112. Current population PK dataset is too limited to recommend dose adaptations and to assess the B/R ratio in patients with moderate hepatic insufficiency. Therefore, ponesimod is not recommended treatment in patients with moderate hepatic impairment. Ponesimod is contraindicated in patients with severe hepatic impairment due to the 3-fold increase in exposure of ponesimod and the risk of hepatobiliary disorders/liver enzyme abnormalities (see clinical safety).

In vitro studies showed that ponesimod and its metabolite M13 have a low potential for interactions. Although M12 is the most abundant metabolite in excreta, it has not been investigated in the *in vitro* interaction studies as the concentration of M12 is <10% of the total amount present in plasma. Further, although the clinical drug interaction studies AC-058-104 and AC-058-117 were not specifically designed to investigate specific model substrates, these studies support that the risk of PK drug interactions related to CYP3A4 and CYP2D6 is low. The applicant has not evaluated whether ponesimod is a substrate for transporters but adequately justified that no clinically relevant transporter interactions are expected. No clinically relevant interaction with the hepatic uptake transporters OCT1, OCT3 and hepatic efflux transporter MATE-1 is expected based on limited amount of unchanged drug eliminated via hepatic secretion, the good passive cell permeability of ponesimod and non-clinical study results that indicate the lack of involvement of active transport into the hepatocytes. No clinically relevant interaction with the renal uptake transporters OCT3, OAT1 and OAT3, and efflux transporter MATE2K are expected as ponesimod is not excreted renally (<1% of administered dose).

Although ponesimod displays pH-dependent dissolution, the CHMP agreed with the applicant position that the potential DDI risk of ponesimod with pH modulators is considered to be low and therefore, no DDI study with a drug that increases gastric pH is required.

No dedicated PD studies were performed. PD data and PK/PD data are available from the Phase 2 dose-finding study AC-058B201 and the pivotal Phase 3 study AC-058B30, and in addition, four PK studies provided PD data on cardiac effects.

Ponesimod is an S1P modulator, with high affinity to $S1P_1$ and selectivity for this receptor over other S1P. Ponesimod leads to internalisation of the $S1P_1$ receptor where it is degraded by the intracellular proteasomal system. As a consequence, lymphocytes (T and B cells) are deprived of the necessary signal to egress from lymphoid organs, leading to a reduction of circulating lymphocytes. T and B cells are most sensitive to ponesimod-mediated sequestration. In contrast, monocyte, natural killer (NK) cell, and neutrophil counts are not reduced by ponesimod. The mechanism of action is sufficiently studied and described.

Ponesimod induced a dose-related decrease in lymphocytes levels in the blood. Observed maximal reduction at 20 mg/day was 74%. Maximum predicted reduction in the PK/PD model in total lymphocytes was 87%. In the PK/PD model, parameters were estimated with adequate precision, except for NK cells, which were not clearly affected by ponesimod. A limited number of outliers was excluded from the analysis. The exclusions were due to conditional weighted residuals being > 6. This was in accordance with the Analysis Plan.

The effects described above were confirmed in both clinical studies in patients with RMS, where a rapid decline in peripheral lymphocyte counts was observed, which remained thereafter stable until treatment withdrawal. Lymphocyte counts returned close to baseline values within one month after stopping treatment. For the majority of subjects, lymphocyte counts return to normal within 2 weeks.

In the dose-response study B201, the reduction in lymphocyte counts generally needed for therapeutic response, i.e. approximately 70%, was reached with the 20 mg and 40 mg doses. This supports rejecting the 10 mg dose from further studies.

The E-R modelling on data from the dose-response study B201 demonstrated a clear E-R relationship in terms of Gd+ lesions. The predicted decrease in cumulative new Gd+ lesions suggests only a small additional benefit of higher than 20 mg doses. The additional decrease of approximately 10% in ARR with the 40 mg dose as compared to 20 mg can be considered substantial; however, based on the clear dose-response relationship in AE, this additional benefit is not considered such that would justify the 40 mg dose. Also, the E-R modelling based on data from study B301 suggests a clear exposure-response in terms of CUALs within the exposure range observed for 20 mg maintenance dose of ponesimod.

Bradycardia and AV block are known secondary pharmacological effects of S1P modulators. Therefore an up-titration regimen should be used. The applicant investigated two up-titration regimens, one starting at 2mg dose and one with a starting dose of 10mg. The applicant also constructed a popPK/PD model based on the phase 1 studies, which included 280 healthy subjects, with 9529 ponesimod plasma concentrations and 42,559 HR measurements. This is sufficient to accurately design a popPK/PD model. This model is used to substantiate the proposed up-titration regimen and to include safety warnings on concomitant with beta-blockers.

Overall, it is agreed with the applicant that the effect of ponesimod on the HR is dose-dependent. The applicant concluded that gradual up-titration leads to a reduced risk of bradycardia due to development of tolerance can also be agreed. However, for this conclusion also the safety data from the phase 2 and 3 study has to be taken into account. In the SmPC, the applicant proposes a warning for subjects with a baseline HR $\leq$55bpm based on the simulation. This warning in section 4.4 can be supported.

Ponesimod shows a reduction of FEV_1 in dose and exposure-related manner. In addition, an effect of sex, age, race and baseline EDSS was observed on the FEV_1. However, it is agreed with the applicant that no dose adjustment is required for sex, age, race and baseline EDSS, as these were not associated with the magnitude of the effect of ponesimod on FEV_1. However, long-term treatment with ponesimod poses a risk, particularly in respiratory compromised subjects. Therefore, a warning in relation with the effect on pulmonary function has been included in the SmPC and bronchoconstriction has been added as important identified risk in the risk management plan (RMP).

2.4.5. Conclusions on clinical pharmacology

The PK of ponesimod and its metabolites has been adequately characterised in healthy volunteers and the intended patient population.

The mechanism of action of ponesimod is adequately described, and its effects on lymphocytes, HR and pulmonary function addressed. The proposed clinical dose of ponesimod 20 mg preceded by 14 days of titration was documented.

2.5. Clinical efficacy

Table 5: Overview of dose-response and main clinical studies

Study ID	Design	Study Posology	Study Objective	Subjs by arm entered/ compl.	Duration	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoint
Phase 2 studies								
B201	Double-blind, randomised, parallel group, placebo-controlled study in adults.	Ponesimod 10 mg QD Ponesimod 20 mg QD Ponesimod 40 mg QD Placebo QD.	Efficacy, safety and tolerability	Randomised total: 464 Ponesimod 10 mg: 108 Ponesimod 20 mg:116 Ponesimod 40 mg: 119 Placebo: 121	Screening: up to 35 days Double-blind: 24 weeks	Male 32.5% Median age 36	Patients with Relapsing Remitting Multiple Sclerosis	Cumulative number of new Gd+ lesions over Weeks 12, 16, 20, and 24
B202 (ongoing)	Double-blind, randomised, parallel-group extension to study B201	Treatment Period 1: Ponesimod 10 mg QD Ponesimod 20 mg QD Ponesimod 40 mg QD Treatment Period 2: Ponesimod 10 mg QD Ponesimod 20 mg QD Treatment Period 3: Ponesimod 20 mg QD	Safety, tolerability and efficacy	Enrolled Treatment Period 1: 353 subjects Enrolled Treatment Period 2: 305 subjects Enrolled Treatment Period 3: 228 subjects Included in the interim analysis (data cut-off 31 March 2019): 435 subjects Ponesimod 10 mg: 139 Ponesimod 20 mg: 145 Ponesimod 40 mg: 151	Up to 528 weeks (up to 96 weeks in Treatment Period 1 and up to 432 weeks in Treatment Periods 2 & 3)	Male 32.2% Median age 36	Patients with Relapsing Remitting Multiple Sclerosis	
Phase 3 studies								
B301	Double-blind, randomised, parallel-group, active-controlled study in adults	Ponesimod 20 mg QD Teriflunomide 14 mg qd	Efficacy, safety	Randomised total 1133 Ponesimod 20 mg: 567 Teriflunomide 14 mg: 566	108 weeks	Male 35.1% Median age 37	Patients with Relapsing multiple sclerosis	ARR
B303 (ongoing)	Open-label extension of B301	Ponesimod 20 mg QD.	Safety, tolerability and long-term efficacy	Enrolled: 877 subjects (B301 Ponesimod 20 mg: 439 B301 teriflunomide 14 mg: 438) Included in the interim analysis (cut-off date of 30 May 2019): 877	Up to 240 weeks	Male 34.3% Median age 39	Patients with Relapsing multiple sclerosis	

2.5.1. Dose response study

Study B201 was a prospective, multicentre, randomised, double-blind (DB), placebo-controlled, parallel-group, dose-finding study, in which efficacy, safety, and tolerability of 3 doses of ponesimod (10, 20, or 40 mg) administered for 24 weeks were investigated in subjects with RRMS. The dose selection for this study was based on both efficacy and safety considerations, based on data from Phase 1 single-ascending

and multiple-ascending dose studies. In this study, dose increments were performed in a weekly interval for patients randomised in the 20 mg and 40 mg dose groups.

The study included patients aged 18 to 55 years with a diagnosis of RRMS according to the revised (2005) McDonald Diagnostic Criteria for MS. Patients were required to have ≥1 documented relapse(s) within 12 months prior to screening or ≥2 documented relapses within 24 months prior to screening or at least 1 Gd+ lesion detected on T1-weighted MRI (central reading) at screening. EDSS score of 0 to 5.5 (inclusive) at screening was required. Both treatment-naïve and patients previously treated with IFN beta-1a, IFN beta-1b, glatiramer acetate, or natalizumab, were eligible to enrol in the study. The study population consisted solely of RRMS patients; this is considered acceptable for demonstrating effect primarily in an MRI endpoint.

The primary efficacy endpoint was the cumulative number of new Gd+ lesions per patient on T1-weighted MRI scans at Weeks 12 to 24. Secondary endpoints included ARR and time to first confirmed relapse. An MRI primary endpoint is accepted for a dose-response study.

464 patients were randomised to the study, with 108, 116, 119, and 121 patients randomised to the ponesimod 10 mg, 20 mg, 40 mg, and placebo groups, respectively (Table 5).

The mean cumulative numbers of new Gd+ lesions from Weeks 12 to 24 were 3.5, 1.1, 1.4 and 6.2 in the ponesimod 10 mg, ponesimod 20 mg, ponesimod 40 mg and placebo groups, respectively. The treatment effect (ratio) vs. placebo with ponesimod 10 mg was 0.566 (95% CIs: 0.337, 0.952, P = 0.0318), with ponesimod 20 mg it was 0.170 (95% CIs: 0.100, 0.289, P < 0.0001), and with ponesimod 40 mg it was 0.226 (95% CIs: 0.133, 0.384, P < 0.0001).

The estimated ARR (confirmed relapses) within 24 weeks of study drug initiation was lower in the ponesimod groups compared to placebo. The treatment effect (ratio) vs placebo with ponesimod 10 mg was 0.632 (95% CIs: 0.332, 1.202, p = 0.1619), with ponesimod 20 mg it was 0.793 (95% CIs: 0.440, 1.432, p 0.4420), and with ponesimod 40 mg it was 0.478 (95% CIs: 0.240, 0.954, p = 0.0363).

Up-titration regimens

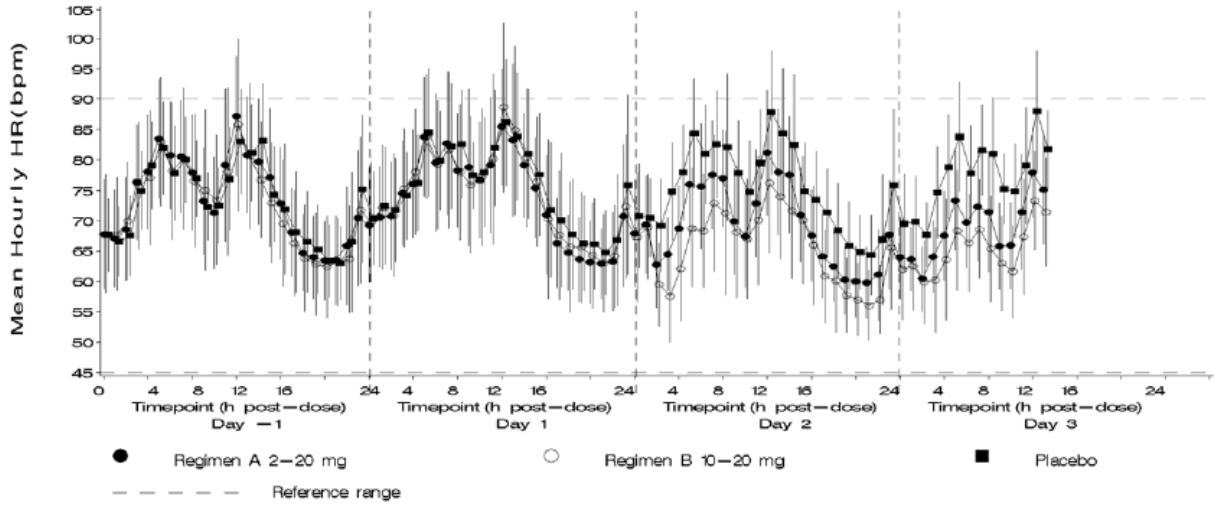
Activation of $S1P_1$ receptors during initiation of treatment with ponesimod leads to dose-dependent transient HR decrease and infrequently delay in AV conduction. In the presence of ponesimod, this initial receptor activation is followed by desensitisation of the $S1P_1$ system in cardiomyocytes leading to normalisation of HR and rhythm. These initial effects on HR and AV conduction are mitigated by initiating treatment with a low dose (2 mg) of ponesimod, followed by a gradual up-titration to the maintenance dose (20 mg).

Study 115 in healthy volunteers was conducted to investigate and optimise the ponesimod up-titration regimen. Two up-titration regimens were compared in a DB, placebo-controlled, randomised, two-way crossover study in 32 subjects (active: placebo ratio of 3:1). The gradual up-titration regimen with a starting dose of 2 mg later used in Studies B301/B303 was designated regimen A, and an up-titration regimen with a starting dose of 10 mg used in Studies B201/B202 was designated regimen B.

The first dose of ponesimod (Day 2) resulted in a transient decrease in mean hourly HR from baseline as assessed by Holter (Figure 6). The decrease was greater with treatment regimen B (maximum mean decrease: 12 bpm) than with regimen A (6 bpm) and placebo (0 bpm). These maximum mean decreases occurred 2–3 h postdose and mean hourly HR had returned to predose values by 4–5 h postdose. On Day 3, the decrease in mean hourly HR from predose induced by ponesimod was similar or smaller when compared to Day 2, and there was no longer a difference between regimens A and B (in absolute and relative terms). For both regimens, the predose mean hourly HR values on Day 3 and later were 5 to 10 bpm lower when compared to baseline and remained lower during the complete ponesimod treatment

period. Taking this decrease in predose values into account, no further postdose decrease in mean hourly HR was observed on Day 3 and later study days in either regimen.

Figure 6: Mean (SD) hourly Holter HR data over Days-1 to 3 (Per protocol set) (Ponesimod Protocol:AC-058-115)



For the placebo group, data from periods1 and 2 are pooled together.

Similar effects of ponesimod on HR were observed with 12-lead ECGs. The maximum mean decreases from baseline in HR on Day 2 (after the first dose of ponesimod) were 13 bpm for regimen B, 9 bpm for regimen A, and 4 bpm for placebo, and occurred 2 h after administration in all treatment groups.

HR values of interest (HR <45 bpm, and/or decrease from baseline in HR of >20 bpm from 12 lead ECG) were recorded more frequently in ponesimod-treated subjects when compared to placebo (12-lead ECG, HR <45 bpm; regimen A: 12.5% of subjects, regimen B: 16.7%, placebo: 0% / HR decrease from baseline >20 bpm; regimen A: 8.3%, regimen B: 8.3%, placebo: 6.3%). HR<45 bpm and decrease from baseline of >20 bpm following the first ponesimod dose occurred more frequently during regimen B (16.7%) than regimen A (4.2%). Whereas 3 subjects during regimen B experienced an HR value <40 bpm, no such values were recorded during regimen A or placebo. Similar results were obtained from Holter.

The percentage of subjects (events), with PR interval values ≥200 ms was 29.2% (221), 29.2% (258), and 25.0% (112) in regimen A, B, and placebo, respectively. The percentage of subjects (events), with an increase from baseline in PR interval of >20 ms was 25.0% (63), 33.3% (44), and 18.8% (8) in regimen A, B, and placebo, respectively.

The proportion of subjects who experienced an AV block (defined as PR >210 ms) was 25% for all treatment groups. However, the total number of occurrences of any AV block was largest during regimen B (143) followed by regimen A (79) and placebo (33). The maximum observed PR intervals were 222 ms (Day -1, predose), 236 ms (Day 4, 3 h), and 220 ms (Day -1, 2 h) in regimen A, B, and placebo, respectively.

For the placebo group, the occurrence of any AV block appeared to be evenly distributed over the study days whereas, for both regimens A and B, most AV blocks were observed during the first 6 8 days of treatment with ponesimod. Second degree AV block Mobitz I was observed (12 lead ECG) in 1 subject during regimen B (Day 9, predose, second period) and in 2 subjects in the placebo treatment group. No

second-degree AV block Mobitz I was observed during ponesimod treatment in regimen A. In addition, 1 AE of second-degree AV block Mobitz I on Day 1 during the night following administration of placebo during regimen A (from Holter) was reported.

Fewer and less pronounced ponesimod-related cardiodynamic effects were observed in the gradual up-titration regimen starting with ponesimod 2 mg compared to the up-titration regimen starting with ponesimod 10 mg.

2.5.2. Main study

Study AC-058B301 (B301)

Methods

Study B301 was a multicentre, randomised, DB, parallel-group, active-controlled, superiority study to compare the efficacy and safety of ponesimod to teriflunomide in subjects with Relapsing Multiple Sclerosis.

The study included three periods: a pre-randomisation period of up to 45 days, a treatment period of 108 weeks and a follow-up phase of 30 days.

Study Participants

The key inclusion criteria were

- Males and females aged 18 to 55 years (inclusive).
- Presenting with a diagnosis of MS as defined by the revised (2010) McDonald Diagnostic Criteria for MS with relapsing course from onset (i.e. RRMS, or SPMS with superimposed relapses).
- Subjects who had experienced one or more documented MS attacks with onset within the period of 12 to 1 months prior to baseline EDSS assessment, or two or more documented MS attacks with onset within the period of 24 to 1 months prior to baseline EDSS assessment, or had one or more Gd+ lesion(s) of the brain on an MRI performed within 6 months prior to baseline EDSS assessment (MRI assessed at Visit 2 [Baseline] could be the qualifying scan).
- Treatment-naïve or previously treated with IFN beta-1a, IFN beta-1b, glatiramer acetate, natalizumab, or dimethyl fumarate.
- Ambulatory and with an EDSS score between 0 and 5.5 (inclusive) at Visit 1 (Screening) and Visit 2 (Baseline).
- Subject who agreed to use an accelerated elimination procedure for teriflunomide after the last dose of study drug.

The key exclusion criteria were

- Lactating or pregnant women.
- Subjects with a diagnosis of MS with progressive course from onset (i.e. primary progressive or progressive relapsing MS).

- Subjects with significant medical conditions or receiving therapies for such conditions (e.g. cardiovascular, pulmonary, immunological, hepatic, ophthalmological, ocular, and malignancy) were not eligible to enter the study.
- Subjects with contraindications to MRI or with clinically relevant medical or surgical conditions that, in the opinion of the investigator, would put the subject at risk by participating in the study were not eligible to enter the study.
- Subjects who were unlikely to comply with the protocol were not eligible to enter the study.

Treatments

Subjects who met all inclusion criteria and none of the exclusion criteria were randomised to either ponesimod or teriflunomide treatment.

During Days 1 to 14 (up-titration period), one tablet of ponesimod 2, 3, 4, 5, 6, 7, 8, 9, or 10 mg (or matching placebo) was to be taken orally once daily. The matching placebos for these doses were supplied as identical tablets. During the maintenance period (Day 15 until end of treatment [EOT]), one over-encapsulated tablet of ponesimod 20 mg was to be taken orally once daily.

The up-titration phase of the study was conducted in a double-dummy fashion, while the maintenance phase was active-controlled without a double-dummy design.

To accelerate the reduction of teriflunomide plasma concentrations at the end of DB treatment, all subjects underwent an accelerated teriflunomide elimination procedure at end-of-treatment (EOT), using either cholestyramine or activated charcoal. Due to blinding, all subjects, including those who had received ponesimod 20 mg treatment, underwent this procedure.

Objectives

The primary objective of the study was to determine whether ponesimod is more efficacious than teriflunomide in terms of reducing relapses in subjects with RMS.

Secondary objectives were to assess the effect of ponesimod on disability accumulation and on other aspects of MS disease control, and to assess the safety and tolerability of ponesimod in subjects with RMS.

Outcomes/endpoints

The **primary efficacy endpoint** was ARR up to EOS, defined as the number of confirmed relapses according to the treating neurologist/principal investigator per subject-year.

A relapse was defined as new, worsening or recurrent neurological symptoms that occurred at least 30 days after the onset of a preceding relapse, and that lasted at least 24 hours, in the absence of fever or infection. A relapse was confirmed by the treating neurologist only when the subjects' symptoms were accompanied by an increase in EDSS/ Functional Systems [FS] scores, which was consistent with the subject's symptoms, from a previous clinically stable EDSS/FS assessment (i.e., performed at least 30 days after the onset of any previous relapse), obtained by the efficacy assessor and consistent with the following:

- An increase of at least half a step (0.5 points; unless EDSS=0, then an increase of at least 1.0 points was required) or

- An increase of at least 1.0 point in at least two FS scores, or
- An increase of at least 2.0 points in at least one FS score (excluding bladder/bowel and cerebral).

The **secondary efficacy variables** were:

- Change from baseline to Week 108 in fatigue-related symptoms as measured by the symptoms domain of the FSIQ–RMS (a Patient-Reported Outcome [PRO] developed by the applicant].
- CUALs from baseline to Week 108.
- Time to 12-week CDA from baseline to EOS.
- Time to 24-week CDA from baseline to EOS.

Several MRI based and exploratory clinical endpoints were defined, including for example the percent change in brain volume from baseline to Week 108, the cumulative number of new or enlarging T2 lesions from baseline to Week 108, time to first confirmed relapse, change from baseline by visit up to Week 108 in EDSS and No Evidence of Disease Activity (NEDA)-3 and NEDA-4 status up to end of the study. NEDA-3 was defined as absence of confirmed relapse, Gd+ lesions, new or enlarging T2 lesions, and 12-week CDA from baseline up to the specified time point. NEDA-4 adds no brain volume change.

Sample size

The **sample size** for the study was estimated by simulation using negative binomial (NB) distribution. A sample size of 1100 subjects (550 per treatment group) provides a power of approximately 90% for a significance level of 0.01, under the assumption that ARR is 0.320 for teriflunomide 14 mg and 0.215 for ponesimod 20 mg (which corresponds to a rate reduction of 33%) and using a dispersion=0.9. An annual dropout rate of approximately 15% was assumed for the first year and 7.5% for the second year.

Randomisation

Subjects were randomly assigned in a 1:1 ratio to receive ponesimod or teriflunomide based on a computer-generated randomisation schedule. The randomisation was balanced by using permuted blocks of 6 subjects per block.

Blinding (masking)

Study drug blinding

The investigator and study staff, the subjects, the monitors, all sponsor Clinical Trial Team members and CROs involved in the conduct of the study remained blinded to the treatment until study closure. The investigational treatment and active comparator, and their respective matching placebos (during the initial up-titration stage when study drug treatments were administered in a double-dummy fashion) were indistinguishable, and all subject kits were packaged in the same way.

Functional blinding

First-dose effects on HR and AV conduction, lymphocyte count reduction, and teriflunomide plasma concentration were identified as potentially unblinding information. After administration of the first dose on Day 1 and on the first day of re-initiation of study drug, post-dose monitoring was performed by an independent first-dose administrator.

Data including ECG variables, blood pressure and AEs (if applicable) were reported in a separate electronic case report form (eCRF) and processed by independent data managers and statisticians. The

primary endpoint (ARR) and disability accumulation are based on the evaluations of the EDSS and FS scores, assessed by an efficacy assessor, not involved in any other aspects of patient care and management throughout the study.

During the procedure, the applicant was requested to clarify whether the same physician performed the EDSS evaluations at baseline and over the study as indicated in the EMA guideline EMA/CHMP/771815/2011. The applicant provided data showing that for more than 80% of subjects, the same EDSS assessor as at baseline conducted the EDSS assessments throughout the study. Additionally, the applicant performed a sensitivity analysis to estimate the risk for a 12-week CDA event and 24-week CDA event derived only on EDSS scores from the same assessor as baseline showing similar results. The clarifications presented by the applicant were considered sufficient.

Statistical methods

Four main **analysis sets** were defined:

- Screened Analysis Set: all subjects who were screened and received a subject number.
- Full Analysis Set (FAS): all randomised subjects.
- The per-protocol (PPS) set: all subjects in the FAS not affected by major protocol deviations.
- The safety analysis set: all subjects who received at least one dose of study treatment.

The primary **estimand** was defined by the following components:

- Population: Subjects with RMS, as defined by the inclusion/exclusion criteria of the study.
- Variable: ARR (number of confirmed relapses per subject-year) up to EOS
- Intercurrent events with corresponding strategies:
    - Treatment discontinuation: Treatment Policy Strategy; including all confirmed relapses regardless of treatment discontinuation.
    - Start of alternative DMTs for MS: Treatment Policy Strategy; including all confirmed relapses, regardless of start of alternative DMTs.
    - Study discontinuation: Hypothetical Strategy; effect if all subjects remained on study as planned per protocol.
- Summary Measure: Rate ratio of ponesimod versus teriflunomide.

Main analysis method

The **primary analysis** was performed up to EOS based on the FAS using an NB regression model for confirmed relapses, with treatment as a factor and the binary stratification variables (EDSS 3.5 versus EDSS >3.5; DMT within last 2 years prior to randomisation [Yes/No]) and the number of relapses in the year prior to study entry (categories ≤1 [or missing, in order to avoid excluding subjects from the analysis] and ≥2) included in the model. The model also included an offset variable defined as the log of time on the study (in years) from randomisation up to EOS. The primary null hypothesis will be tested with a two-sided alpha level of 1% for conclusive evidence and 5% for a positive study.

Mean model-based estimates of the ARR (for confirmed relapses), by treatment arm, as well as 99% CIs and 95% CIs are presented. A rate ratio comparing ponesimod 20 mg with teriflunomide 14 mg will be derived from the model including 99% CIs, 95% CIs and the corresponding p-value.

The effects of covariates on the primary analysis were tested using several **sensitivity analyses**: an unadjusted analysis; and an analysis using derived stratification variables. Sensitivity analysis on the missing data handling consisted of: a missing at random (MAR) multiple imputation (MI) approach assuming similar rates before and after withdrawal; two reference-based MI approaches, copy reference using the teriflunomide rate after withdrawal but retaining the treatment effect up to withdrawal, and jump to reference imputing reference rate assuming withdrawn patients will quickly lose any positive effect up to withdrawal; delta-adjustment MI assuming different penalties for the ponesimod and teriflunomide arms.

The **secondary endpoint analysis** for fatigue will be based on the FAS. A mixed-effect model repeated measurements (MMRM) which includes baseline, and the two stratification factors as covariates, treatment (fixed effects), visit, treatment by visit interaction, and baseline by visit interaction are applied. An unstructured co-variance structure shared across treatment groups will be used to model within-patient errors. A generalised linear model with NB distribution as described for the primary analysis will be assumed for the number of CUAL from baseline to Week 108. The main analysis on Time to 12-Week and 24-Week CDA up to EOS will be performed on the FAS by a two-sided stratified log-rank test with stratification factors as stratification variables and a stratified Cox regression will be provided.

A **multiple testing strategy** was applied, which started with testing the primary endpoint at full alpha, followed hierarchically by a fall-back type procedure for the secondary endpoints. If the primary endpoint null hypothesis was rejected, the alpha was to be split evenly (1/3 of alpha) between the first 3 of 4 secondary endpoints, with subsequent reusing alpha after a successful test.

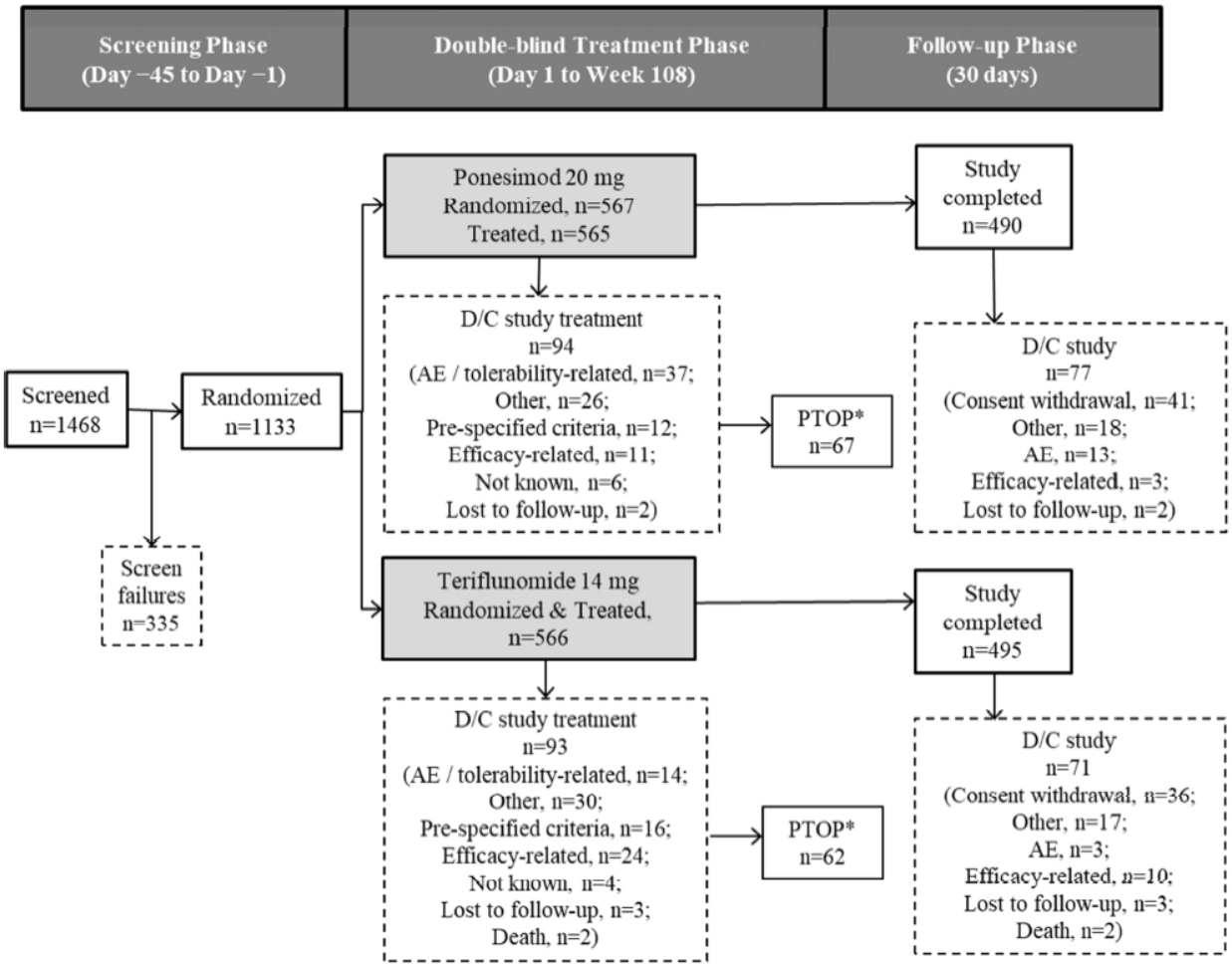
For the primary and all secondary endpoints, the **subgroup analyses** were conducted using the FAS and/or the PPS on the following subgroup variables: baseline EDSS; DMT within last 2 years prior to randomisation; geographical region; gender; age group; MS subtype; Number of relapses in the year prior to study entry; Gd+ lesions at baseline; highly active disease; and recruitment period. A subject was considered to have highly active disease if one or both of the following conditions were fulfilled:

1. Any DMT for MS received within 12 months prior to randomisation and one or both of the following:
    - ≥1 relapse within 1 year prior to study entry and the baseline MRI read centrally showed either ≥1 Gd+ lesion and/or ≥9 T2 lesions
    - Number of relapses within 1 year prior to study entry ≥ number of relapses between 2 and 1 year prior to study entry, for subjects with at least one relapse within 2 years prior to study entry.
2. ≥2 relapses within the 1 year prior to study entry and baseline EDSS score >2 and baseline MRI read centrally showed ≥1 Gd+ lesion.

Results

Participant flow

Figure 7: Subject disposition in study B301



* Subjects stayed in study beyond safety follow-up.
AE=adverse event; D/C=discontinued; PTOP=posttreatment observation period.

Recruitment

- Date first subject signed informed consent: 13 July 2017
- Date of last observation included in interim analysis: 30 May 2019

Conduct of the study

There were 6 substantial global amendments to the protocol:

- Amendment 1 (29 Apr 2015 (protocol version 2)) included a clarification was included that MS relapses were not to be considered as AEs. However, this is considered to have no impact on the study conduction as the first patient was screened on 27 April 2015 and the first randomisation date was 04 June 2015.
- Amendment 2 (16 Jul 2015 (protocol version 3) included a clarification on the exclusion criteria based on PML infection suspect as well as changes in a suicide clinical scale and frequency of WBC monitoring.
- Amendment 3 (05 Feb 2016 (protocol version 4) included updates in response to the comments received from the US FDA regarding the assessment of relapses including a standardised stepwise

procedure for the confirmation and reporting of relapses and a clarification concerning the role of the treating neurologist and efficacy assessor in EDSS and FS assessments.

- Amendment 4 (14 Nov 2016 (protocol version 5) included a change in the timing for teriflunomide plasma concentration testing triggered by the observation that 33.0% of all tests conducted showed teriflunomide plasma concentration above the threshold of 0.02 mg/L and thus risking the unblinding of the treatment allocation. At that time, the total number of affected subjects was very low (n=11).
- Amendment 5 (30 Aug 2017 (protocol version 6) allowed testing of teriflunomide plasma concentration in any subject who had discontinued study drug if deemed necessary for the subject's safety, at the discretion of the investigator
- Amendment 6 (05 Dec 2018 (protocol version 7)) revise the multiple testing strategy for the secondary endpoints: (1) The number of secondary endpoints was reduced from five to four as time to first relapse and % change from baseline in BVL were moved from secondary to exploratory and time to 24-week CDA was moved from exploratory to secondary and (2) the multiple testing strategy to control the Type I error for testing secondary endpoints was modified according to a fallback type method to optimise the ability of the trial to achieve its objectives

At least one protocol deviation (PD) was reported for all randomised subjects during the study. Important PDs were reported for 46.7% and 47.0% of subjects in the ponesimod 20 mg and teriflunomide 14 mg groups, respectively. PDs related to efficacy and endpoints occurred in ~90% of patients and PDs related to blinding in 15% of patients. The distribution of important PDs across the two treatment groups was well-balanced except for efficacy/endpoint category reported with a higher frequency was reported for the teriflunomide 14 mg groups. According to the applicant, this imbalance can be explained by a higher occurrence of relapses in the teriflunomide 14 mg group. Upon request, the applicant has provided a thorough overview and impact assessment of PDs related to efficacy assessments and blinding, thereby addressing the study integrity. It is acknowledged that the overall complexity of the study with two data sets and numerous assessment points of several endpoints, and the policy on reporting PDs may have influenced the high number of reported PDs. The proportion of important PDs is similar to other recent MS trials which is reassuring. The performed sensitivity analyses show that excluding patients with important PDs related to efficacy/endpoints and blinding do not impact the overall conclusions of the study.

Mean compliance with study treatment in both treatment groups was 99% and less than 80% compliance with study treatment was reported for a total of 7 subjects (0.6%) and these were excluded from the PPS.

Baseline data

Overall, the study population was predominantly White (97.4%) and 64.9% of subjects were female. The median age was 37.0 years (range 18 to 55 years). The mean body mass index at baseline 24.7 kg/m_2. Most of the subjects were enrolled at centres in Europe, with 50.6% from EU countries + UK and 41.7% from non-EU European countries plus Russia (Table 6).

The study population predominantly included RRMS subjects (97.4%) with a mean (median) time since first MS symptoms to randomisation in the study of 7.64 (5.77) years. The mean baseline EDSS score was 2.6. The median time since the most recent relapse at screening was 4.27 months and 42.6% (39.9% on ponesimod 20 mg, 45.4% on teriflunomide 14 mg) of subjects had at least one Gd+ T1 lesion at baseline. The proportion of subjects who had received any DMTs within 24 months prior to

randomisation was 37.4%. Approximately 35% of subjects were considered to have a highly active disease at baseline (Table 7) (see definition of highly active disease in methods).

Table 6: Demographic Characteristics in study B301 (FAS population)

	Ponesimod 20 mg N=567	Teriflunomide 14 mg N=566	Total N=1133
Sex [n (%)]			
n	567	566	1133
Male	204 (36.0)	194 (34.3)	398 (35.1)
Female	363 (64.0)	372 (65.7)	735 (64.9)
Age (years)			
n	567	566	1133
Mean	36.7	36.8	36.7
SD	8.74	8.74	8.74
Median	36.0	37.0	37.0
Q1, Q3	30.0, 44.0	30.0, 44.0	0.0,44.0
Min, Max	18, 55	18, 55	18, 55
Race [n (%)]			
n	567	566	1133
American Indian or Alaska Native	0	1 (0.2)	1 (0.1)
Black or African American	3 (0.5)	2 (0.4)	5 (0.4)
White	551 (97.2)	553 (97.7)	1104 (97.4)
Other	5 (0.9)	2 (0.4)	7 (0.6)
Not applicable	8 (1.4)	8 (1.4)	16 (1.4)
Baseline body mass index (kg/m2)			
n	565	566	1131
Mean	24.7	24.6	24.7
SD	4.96	4.81	4.88
Median	23.9	23.8	23.9
Q1, Q3	21.1, 27.1	21.2, 27.0	21.2, 27.1
Min, Max	16, 44	15, 45	15, 45
Geographical region of enrolling site [n(%)]			
European Union (EU) + UK	289 (51.0)	284 (50.2)	573 (50.6)
Europe Non-EU + Russia	233 (41.1)	239 (42.2)	472 (41.7)
North America	32 (5.6)	24 (4.2)	56 (4.9)
Rest of World	13 (2.3)	19 (3.4)	32 (2.8)

min=minimum, max=maximum, Q1=first quartile, Q3=third quartile, SD=standard deviation, UK=United Kingdom

Table 7: Baseline disease in study B301 (FAS population)

	Ponesimod 20 mg N=567	Teriflunomide 14 mg N=566	Total N=1133
Baseline EDSS (from eCRF)			
n	567	566	1133
Mean	2.57	2.56	2.56
SD	1.174	1.229	1.201
Median	2.50	2.50	2.50
Q1, Q3	1.50, 3.50	1.50, 3.50	1.50, 3.50
Min, Max	0.0, 5.5	0.0, 5.5	0.0, 5.5
Any MS DMT received prior to randomisation [n (%)]			
n	567	566	1133
Yes	243 (42.9)	245 (43.3)	488 (43.1)
No	324 (57.1)	321 (56.7)	645 (56.9)
Any DMT(a) received within 2 years prior to randomisation [n (%)]*			
n	567	566	1133
Yes	213 (37.6)	211 (37.3)	424 (37.4)
No	354 (62.4)	355 (62.7)	709 (62.6)
Time since first symptoms (years) at randomisation			
n	567	566	1133
Mean	7.63	7.65	7.64
SD	6.781	6.782	6.779
Median	5.84	5.70	5.77
Q1, Q3	2.40, 10.97	2.24, 11.03	2.32, 11.01
Min, Max	0.2, 40.8	0.2, 30.8	0.2, 40.8
Time since most recent relapse (months) at screening			
n	562	557	1119
Mean	5.41	5.04	5.23
SD	4.005	3.719	3.868
Median	4.47	4.07	4.27
Q1, Q3	2.56, 7.33	2.10, 7.13	2.37, 7.26
Min, Max	0.2, 44.9	0.3, 26.2	0.2, 44.9
Number of relapses in last year prior to study entry			
n	567	565	1132
Mean	1.2	1.3	1.3
SD	0.61	0.65	0.63
Median	1.0	1.0	1.0
Q1, Q3	1.0, 1.0	1.0, 2.0	1.0, 1.0
Min, Max	0, 4	0, 5	0, 5
Multiple Sclerosis subtype [n (%)]			
n	567	566	1133
RRMS	552 (97.4)	552 (97.5)	1104 (97.4)
SPMS	15 (2.6)	14 (2.5)	29 (2.6)
Presence of Gd+ T1 lesions at baseline (from central reader) [n (%)]			
n	567	564	1131
Yes	226 (39.9)	256 (45.4)	482 (42.6)
No	341 (60.1)	308 (54.6)	649 (57.4)
Number of T2 lesions at baseline (from central reader)			
n	566	564	1130
<9	63 (11.1)	45 (8.0)	108 (9.6)
>=9	503 (88.9)	519 (92.0)	1022 (90.4)
Volume of T2 lesions at baseline [mm3] (from central reader)			
n	565	563	1128
Mean	8301.4	9489.2	8894.3
SD	10346.28	11265.42	0826.32
Median	4841.3	5651.0	5171.7
Q1, Q3	1679.6, 11004.4	2022.9, 12978.7	1851.3, 11754.1
Min, Max	0, 86053	0, 82776	0, 86053
Highly active disease [n (%)]			
n	567	566	1133
Yes	202 (35.6)	200 (35.3)	402 (35.5)
No	365 (64.4)	366 (64.7)	731 (64.5)

DMT= MS disease modifying therapy, EDSS=Expanded Disability Status Scale, Gd+ =gadolinium-enhancing, max=maximum, min=minimum, Q1=first quartile, Q3=third quartile, RRMS=relapsing-remitting multiple sclerosis, SD=standard deviation, SPMS=secondary progressive multiple sclerosis.

Numbers analysed

Overview of patients included in the main analysis sets is presented in Table 8.

Table 8: Overview of main analysis sets, study B301

	Ponesimod 20 mg (N=567) n (%)	Teriflunomide 14 mg (N=566) n (%)	Total (N=1133) n (%)
Full analysis set	567 (100.0)	566 (100.0)	1133 (100.0)
Safety set	565 (99.6)	566 (100.0)	1131 (99.8)
Per protocol set	557 (98.2)	559 (98.8)	1116 (98.5)

Outcomes and estimation

NOTE: the results of the study are presented according to the testing hierarchy as defined in the MS guideline EMA/CHMP/771815/2011, Rev. 2, i.e. results on disability progression as a key secondary endpoint after ARR.

ARR

The results of the primary analysis on the FAS using an NB regression model for confirmed relapses are presented in Table 9.

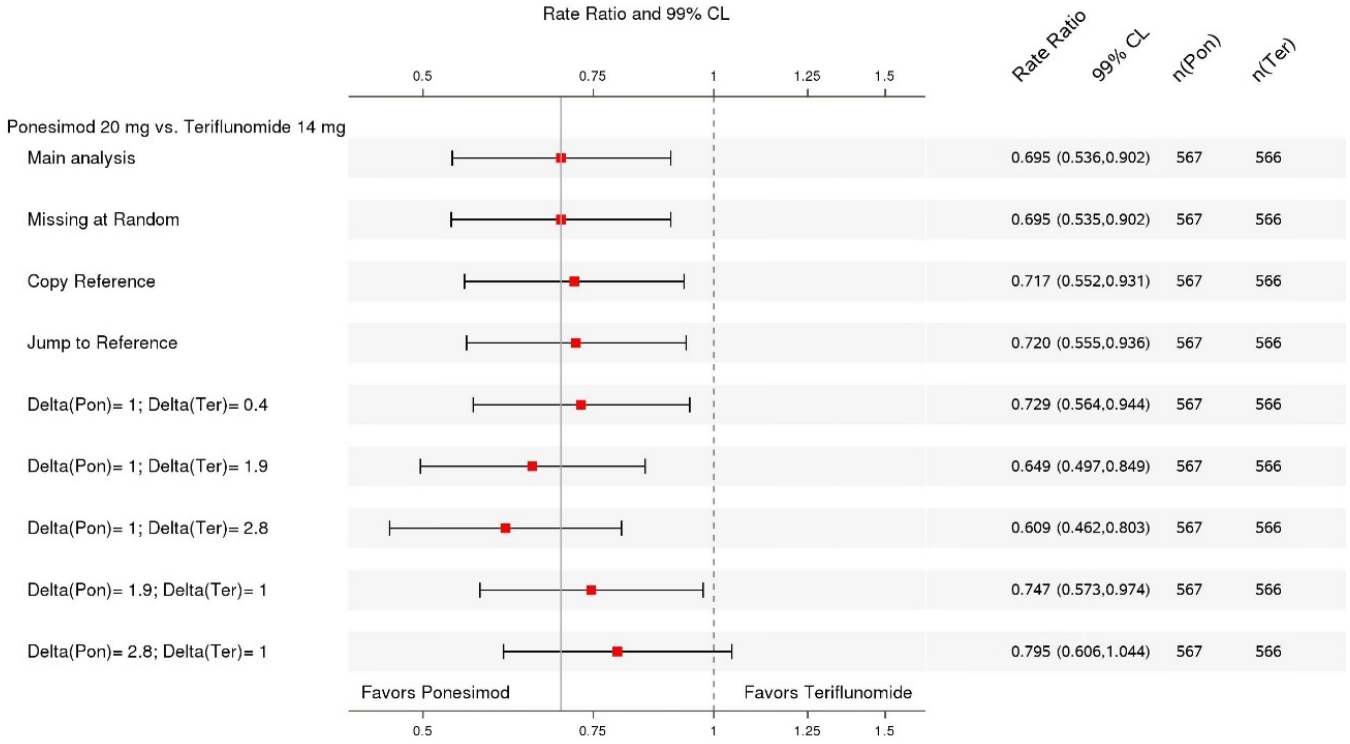
Table 9: Confirmed Relapses up to EOS - ARR From NB Regression

	Ponesimod 20 mg (N=567) n (%)	Teriflunomide 14 mg (N=566) n (%)
Mean estimate (ARR) 99% CIs 95% CIs	0.202 0.165, 0.246 0.173, 0.235	0.290 0.244, 0.345 0.254, 0.331
RR 99% CIs 95% CIs P		0.695 0.536, 0.902 0.570, 0.848 0.0003
Dispersion estimate		0.765
No of subjects included in the analysis Total No of relapses Total time (years) Raw ARR	567 242 1119 0.216	566 344 1137 0.303

Results of the sensitivity analyses were in line with the primary analysis:

- Unadjusted analysis RR 0.706 (99% CIs 0.540, 0.921)
- Adjusted for eCRF-derived stratification variables: RR 0.690 (99% CIs 0.532, 0.896)
- Several sensitivity analyses on missing data, including MAR, copy reference and jump to reference showed consistent results with the primary analysis (Figure 8)

Figure 8: Sensitivity Analysis: Confirmed Relapses up to EOS or Week 108 - MI Between EOS to Week 108 for Subjects With Premature Study Discontinuation, Full Analysis Set

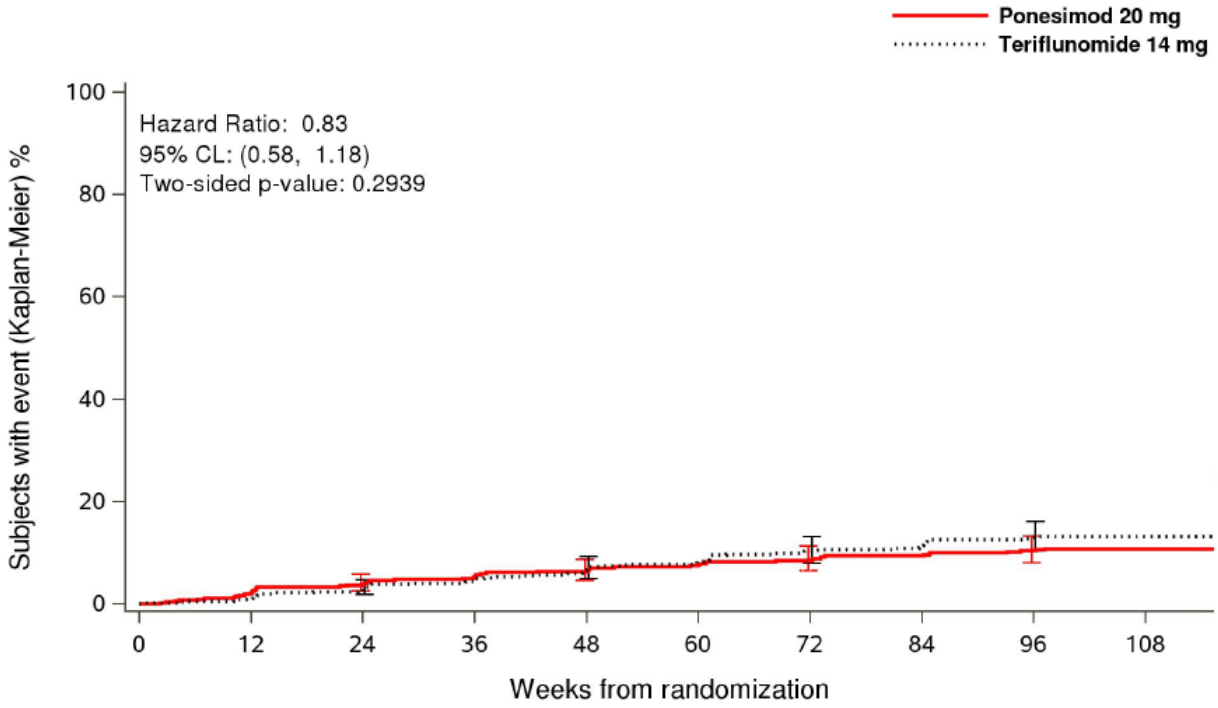


Rate Ratio: ponesimod vs. teriflunomide. Delta(Pon) = multiplicative delta for ponesimod; Delta(Ter) = multiplicative delta for teriflunomide.
Multiple imputation of count data based on Keene et al. 2014 is applied on the number of relapses between EOS and Week 108 for subjects with premature study discontinuation.
Multiple imputed datasets are analysed with a NB model as for the main analysis.

12-week CDA

A 12-week CDA was observed in 10.1% and 12.4% of subjects in the ponesimod 20 mg and teriflunomide 14 mg groups, respectively. The risk for a 12-week CDA event was estimated to be 17% lower with ponesimod 20 mg compared to teriflunomide 14 mg; however, the difference was not found to be statistically significant (Figure 9). Consequently, the formal testing procedure was stopped.

Figure 9: Kaplan-Meier Curve for Time to First 12-Week CDA up to EOS (Main Analysis), Full Analysis Set



Ponesimod 20 mg

at risk	567	533	517	503	492	480	469	458	449	315
event(s)	0	12	21	29	34	41	46	50	55	57
censored	0	22	29	35	41	46	52	59	63	195

Teriflunomide 14 mg

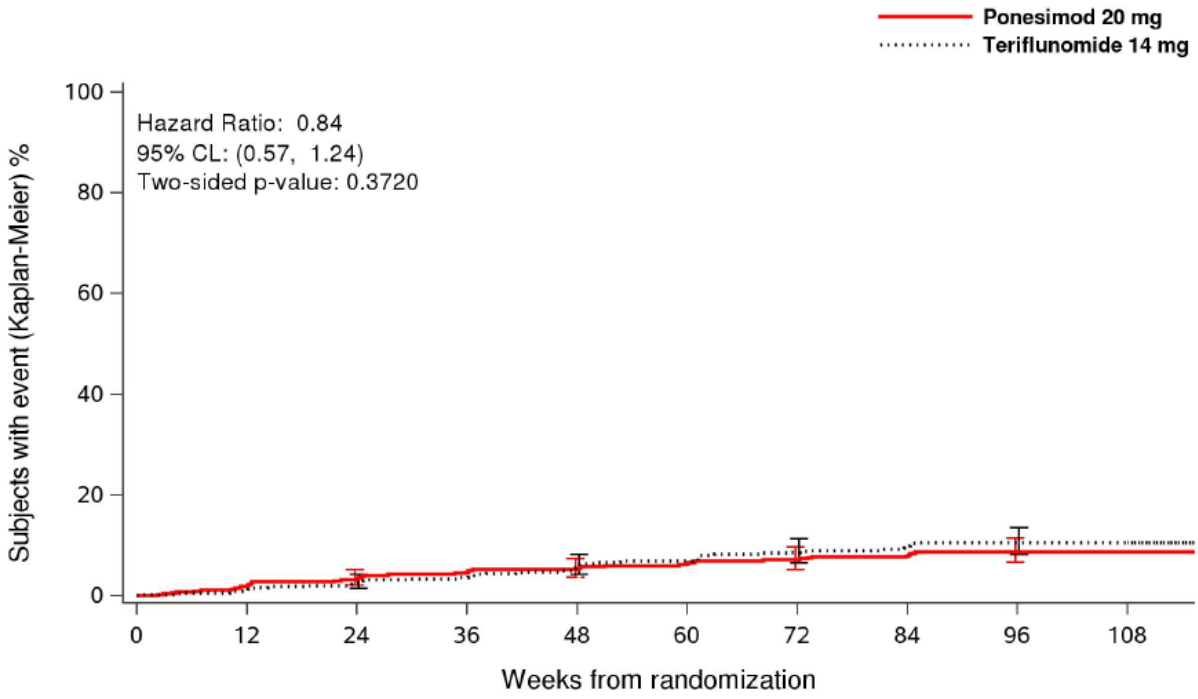
at risk	566	548	528	513	491	481	467	460	439	290
event(s)	0	6	16	24	37	45	55	61	69	70
censored	0	12	22	29	38	40	44	45	58	206

Event = 12-week CDA. Subjects without event are censored at their last EDSS assessment without EDSS increase. Unstratified Kaplan-Meier estimates are presented. Bars on graph display pointwise 95% CIs of the estimate.
P-value is two-sided and based on the stratified log-rank test.
Hazard Ratio estimate obtained from stratified Cox regression with Wald confidence limits. Analysis is stratified by EDSS strata (≤3.5 versus >3.5) and DMT in the last 2 years prior to randomisation strata (Y,N).

<u>24-week CDA</u>

As 12-week CDA analysis did not demonstrate, a statistically significant difference between the treatment groups, 24-week CDA and all subsequent endpoints were handled as exploratory. A 24-week CDA was observed in 8.1% and 9.9% of subjects in the ponesimod 20 mg and teriflunomide 14 mg groups, respectively. The risk for a 24-week CDA event was estimated to be 16% lower for ponesimod 20 mg compared to teriflunomide 14 mg; however, the difference was not statistically significant (Figure 10).

Figure 10: Kaplan-Meier Curve for Time to First 24-Week CDA up to EOS (Main Analysis), Full Analysis Set



Ponesimod 20 mg

at risk	567	534	519	506	497	486	475	464	451	318
event(s)	0	10	18	25	28	34	38	42	46	46
censored	0	23	30	36	42	47	54	61	70	203

Teriflunomide 14 mg

at risk	566	549	530	517	495	488	475	468	446	297
event(s)	0	5	14	20	32	37	46	51	56	56
censored	0	12	22	29	39	41	45	47	64	213

Event = 24-week CDA. Subjects without event are censored at their last EDSS assessment without EDSS increase. Unstratified Kaplan-Meier estimates are presented. Bars on graph display pointwise 95% CIs of the estimate.
P-value is two-sided and based on the stratified log-rank test.
Hazard Ratio estimate obtained from stratified Cox regression with Wald confidence limits. Analysis is stratified by EDSS strata (≤3.5 versus >3.5) and DMT in the last 2 years prior to randomisation strata (Y,N).

FSIQ-RMS

The results on FSIQ-RMS based on the FAS using a MMRM show that the change from baseline to Week 108 was lower in the ponesimod 20 mg group compared with teriflunomide 14 mg (least square [LS] mean: −0.01 for ponesimod 20 mg and 3.56 for teriflunomide 14 mg, an increase from baseline indicates worsening in fatigue symptoms) (Table 10).

Table 10: FSIQ-RMS weekly symptoms score, Change from baseline to Week 108 – MMRM

	Ponesimod 20 mg (N=567) n (%)	Teriflunomide 14 mg (N=566) n (%)
Baseline Mean (SD)	31.9 (20.4)	32.8 (19.1)
Week 108 Mean (SD)	30.5 (21.1)	34.1 (21.5)
No of subjects included in the analysis LS mean 95% CIs	449 -0.01 -1.60, 1.58	458 3.56 1.96, 5.16
Difference of least squares means 95% CIs p-value	-3.57 -5.83, -1.32 0.0019	

FSIQ-RMS=Fatigue Symptom and Impact Questionnaire-Relapsing Multiple Sclerosis, CIs=Confidence Intervals. MMRM models (see methods). A negative change from baseline indicates an improvement in fatigue symptoms.

CUALs

Ponesimod 20 mg reduced the number of CUALs on brain MRIs from baseline to Week 108 by 56% compared to teriflunomide 14 mg (Table 11).

Table 11: Cumulative Number of CUALs from baseline to Week 108 - NB Regression of Lesions per Year

	Ponesimod 20 mg (N=567) n (%)	Teriflunomide 14 mg (N=566) n (%)
Mean no of lesions per year 95% CL	1.405 1.215, 1.624	3.164 2.757, 3.631
RR 95% CL P		0.444 0.364, 0.542 <0.0001
Dispersion estimate		2.409
No of subjects included in the analysis Total No of lesions Total time (years) Raw mean lesions/year	539 1671 1072 1.559	536 3714 1067 3.481

EDSS

The LS mean difference (ponesimod 20 mg – teriflunomide 14 mg) in change from baseline to Week 108 in EDSS score was −0.13 (95% CLs: −0.22, −0.04; p=0.0059), based on repeated measurements analysis of variance (ANOVA) model (MMRM).

Other exploratory endpoints

A summary of other main exploratory efficacy endpoints is presented in Table 12.

Table 12: Summary of Main Exploratory Efficacy Endpoints Results

	Ponesimod 20 mg (N=567)	Teriflunomide 14 mg (N=566)	Ponesimod 20 mg versus Teriflunomide 14 mg
Time to first confirmed relapse	**Subjects with event (%)**		**HR (95% CIs) [p value]**
Up to end-of-study	166 (29.3)	223 (39.4)	0.76 (0.62, 0.93) [0.0081]
Number of new Gd+ lesions	**Mean per scan[$3]**		**RR (95% CIs) [p value]**
From baseline to Week 108	0.18	0.43	0.42 (0.31, 0.56) [<0.0001]
Number of new / enlarging T2 lesions	**Mean per year[$4]**		**RR (95% CIs) [p value]**
From baseline to Week 108	1.40	3.16	0.44 (0.36, 0.54) [<0.0001]
Brain volume	**LS Mean (% change) [$5, ¢5]**		**Difference (95% CIs) [p value]**
From baseline to Week 108	-0.91	-1.25	0.34 (0.17, 0.50) [<0.0001]
NEDA-3	**Estimated Mean (%)[$8]**		**OR (95% CIs) [p value]**
From baseline to Week 108	25.0	16.4	1.70 (1.27, 2.28) [0.0004]
NEDA-4	**Estimated Mean (%)[$9]**		**OR (95% CIs) [p value]**
From baseline to Week 108	11.4	6.5	1.85 (1.24, 2.76) [0.0026]

CIs=confidence intervals, Gd+=gadolinium-enhancing, NEDA=no evidence of disease activity, HR=hazard ratio, LS=least square, RR=rate ratio, OR=odds ratio.
N (included in analysis) for ponesimod and teriflunomide: $3 540 and 538, $4 539 and 536, $5 436 and 434, $8 564 and 568, $9 526 and 532.
N (subjects with Week 108 result) for ponesimod and teriflunomide for MMRM / mixed model analyses: ¢5 376 and 368.

All MRI based endpoints demonstrated a statistically significant difference between the treatment groups, in favour of ponesimod, apart from a change from baseline to Week 108 in the total volume of T1 hypointense lesions (p=0.0619).

Quality of life, SF-36

Results on the SF-36 normative scores (change from baseline to week 108) are presented in Table 13. No formal statistical testing was performed.

Table 13: Quality of life 36-item Short Form Health Survey (SF-36v2): Summary and Domain scores: Changes from baseline to week 108

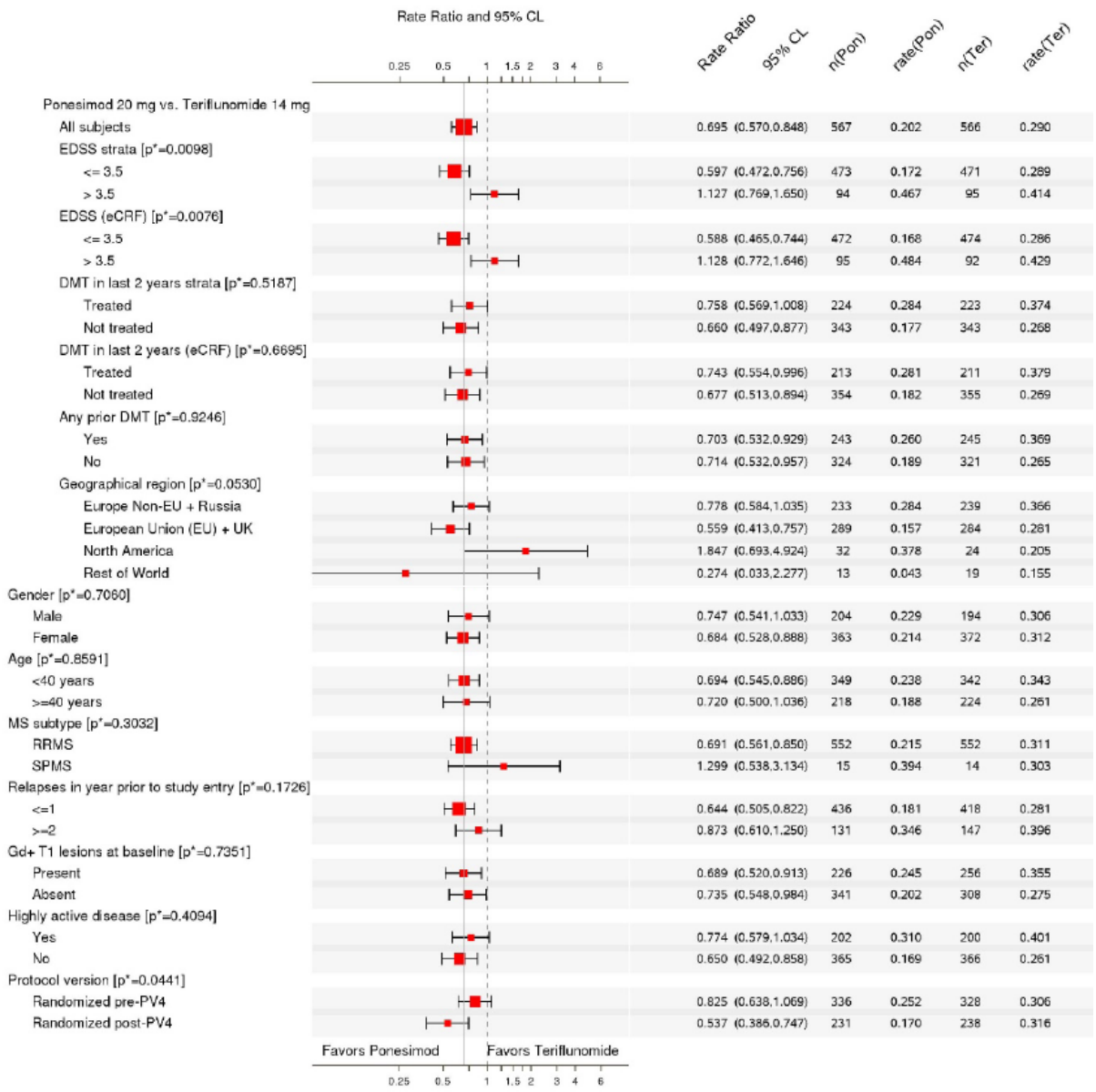
	Ponesimod 20 mg (N=567)	**Teriflunomide 14 mg (N=566)**
Physical functioning normative score, change from baseline		
n	400	394
Mean (SD)	0.05 (7.353)	-0.26 (7.819)
Mental health normative score, change from baseline		
Mean (SD)	-0.14 (10.494)	0.94 (9.729)
Bodily pain normative score, change from baseline		
Mean (SD)	-0.47 (9.248)	-0.45 (9.394)
General health normative score, change from baseline		
Mean (SD)	-0.11 (8.077)	0.05 (8.569)
Social functioning normative score, change from baseline		
Mean (SD)	0.45 (10.261)	-0.50 (9.573)
Vitality normative score, change from baseline		
Mean (SD)	0.47 (8.944)	0.66 (9.7828)

Ancillary analyses

Subgroup analyses

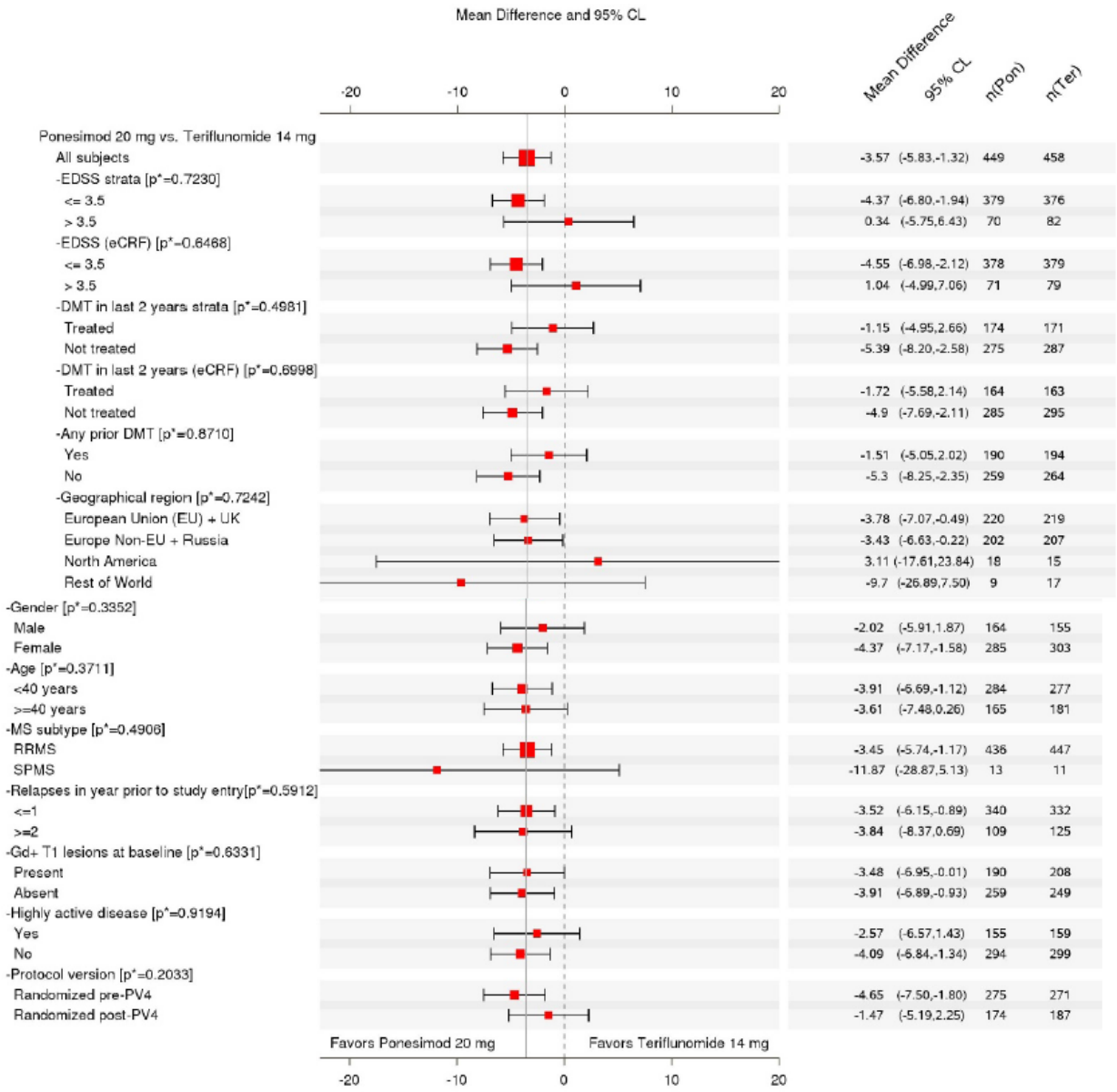
The primary endpoint of confirmed ARR up to EOS was analysed across different pre-defined subgroups (Figure 11). Also secondary endpoints FSIQ-RMS, CUALs and 12-week CDA were assessed across subgroups. The resulted are presented in Figure 12, Figure 13 and Figure 14, respectively.

Figure 11: Subgroup Analysis (95% CIs) of Confirmed ARR up to EOS



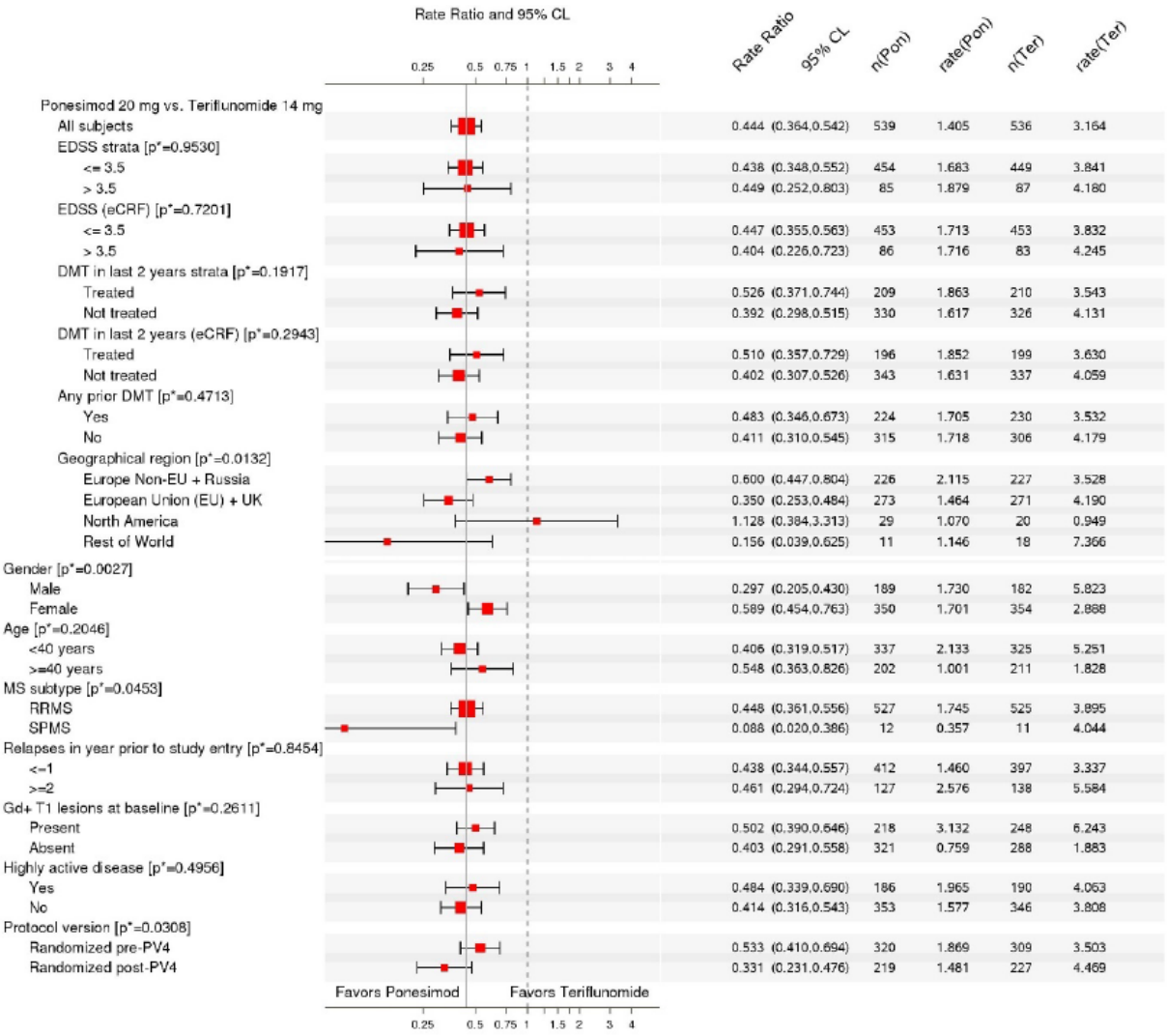
P*=interaction p-value, n(Pon)=No. of subjects in ponesimod group, rate(Pon) = mean rate in ponesimod group, n(Ter)=No. of subjects in teriflunomide group, rate(Ter)=mean rate in teriflunomide group.
NB model is applied with Wald CIs. Offset: log time(years) up to EOS, in each subgroup separately. Interaction p-value from likelihood ratio test of interaction term in model with treatment, subgroup, and treatment by subgroup interactions. The vertical solid line references the treatment effect from the main analysis.
The main analysis is adjusted for the following covariates: EDSS strata (≤ 3.5, > 3.5), DMT in last 2 years prior to randomisation strata (Y, N) and number of relapses in year prior study entry (≤1, ≥2). Analyses in subgroups are not adjusted for covariates.
PV4=protocol version 4, DMT= disease modifying therapy, Gd+ = gadolinium enhancing, EDSS = expanded disability status scale, MS = multiple sclerosis, RRMS = relapsing remitting multiple sclerosis, SPMS = secondary progressive multiple sclerosis.

Figure 12: Subgroup Analysis of Change From Baseline to Week 108 in FSIQ-RMS Weekly Symptoms Score, Full Analysis Set



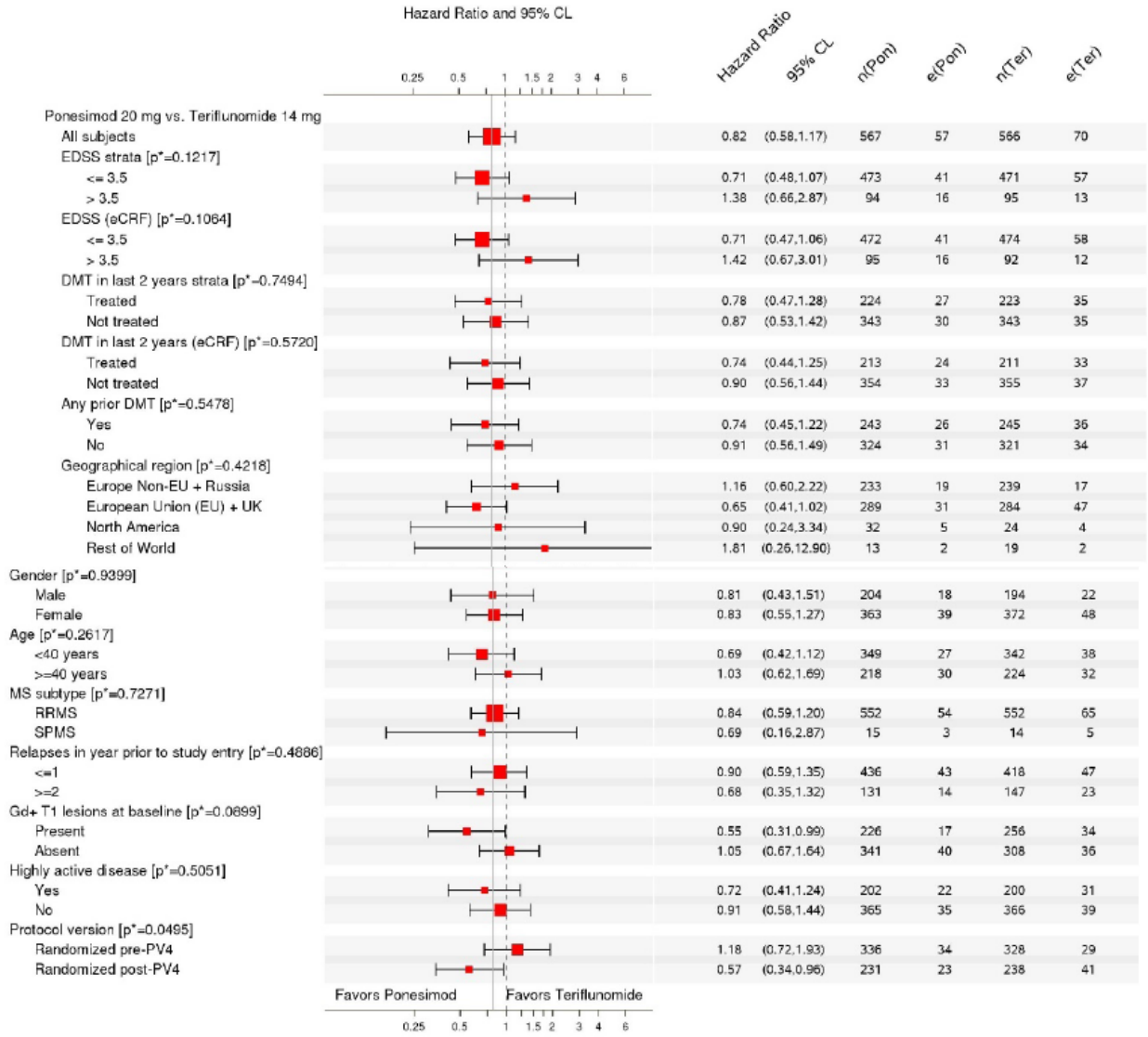
P*=interaction p-value, n(Pon)=No. of subjects in ponesimod group, n(Ter)=No. of subjects in teriflunomide group.
A mixed-effect model repeated measurements (MMRM) with unstructured covariance, treatment, visit, treatment by visit interaction, baseline by visit interaction as fixed effects is applied. Interaction p-value from model with subgroup by treatment interaction. The vertical solid line references the treatment effect from the main analysis. A negative change from baseline indicates an improvement in fatigue symptoms.
Overall = Results from main analysis (adjusted for covariates). Analyses in subgroups are not adjusted for covariates.
FSIQ-RMS=Fatigue Symptom and Impact Questionnaire-Relapsing Multiple Sclerosis, PV4=protocol version 4, DMT= disease modifying therapy, Gd+ = gadolinium enhancing, EDSS = expanded disability status scale, MS = multiple sclerosis, RRMS = relapsing remitting multiple sclerosis, SPMS = secondary progressive multiple sclerosis.

Figure 13: Subgroup Analysis of Cumulative Number of CUALs From Baseline to Week 108, Full Analysis Set



P* = interaction p-value. n(Pon)=No. of subjects in ponesimod group, rate(Pon) = mean CUAL per year rate in ponesimod group, n(Ter)=No. of subjects in teriflunomide group, rate(Ter)=mean CUAL per year rate in teriflunomide group.
NB model is applied with Wald CIs. Offset: log time(years) up to EOS. Interaction p-value from model with treatment, subgroup, and treatment by subgroup interaction. The vertical solid line references the treatment effect from the main analysis.
The main analysis is adjusted for the following covariates: EDSS strata (≤ 3.5, > 3.5), DMT in last 2 years prior to randomisation strata (Y, N) and Gd+ lesions at baseline (Y,N). Analyses in subgroups are not adjusted for covariates.
PV4=protocol version 4, DMT= disease modifying therapy, Gd+ = gadolinium enhancing, EDSS = expanded disability status scale, MS = multiple sclerosis, RRMS = relapsing remitting multiple sclerosis, SPMS = secondary progressive multiple sclerosis.

Figure 14: Subgroup Analysis of Time to First 12-Week CDA up to EOS, Full Analysis Set



P* = interaction p-value. n(Pon)=No. of subjects in ponesimod group, e(Pon) = No. of subjects with event in ponesimod group, n(Ter)=No. of subjects in teriflunomide group, e(Ter)= No. of subjects with event in teriflunomide group.
The vertical solid line references the overall treatment effect from an unstratified Cox regression analysis. Box size is proportional to the number of subjects. Hazard ratio (HR) obtained from Cox regression with Wald CIs.
PV4=protocol version 4, DMT= disease modifying therapy, Gd+ = gadolinium enhancing, EDSS = expanded disability status scale, MS = multiple sclerosis, RRMS = relapsing remitting multiple sclerosis, SPMS = secondary progressive multiple sclerosis.

Comparison to placebo

Additionally, to compare ponesimod 20 mg with placebo and with other DMTs, the applicant has conducted pre-planned analyses using data from study B301 and those of published studies of other DMTs for MS. These include a Matching-Adjusted Indirect Comparison (MAIC) to the Teriflunomide Multiple Sclerosis Oral (TEMSO) study comparing teriflunomide to placebo and a Model-Based Meta-Analysis (MBMA). The results of the MAIC analysis suggest that ponesimod 20 mg reduces the risk of 12-week sustained disability progression by 40% compared to placebo. A reduction of 47% in ARR compared to placebo was observed. The results of the MDMA analysis suggest that in terms of disability progression and relapses, ponesimod positions in the middle of the DMTs included in the analysis.

Summary of main study

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 B/R assessment (see later sections).

Table 14: Summary of Efficacy for trial AC-058B301

Title: AC-058B301			
Study identifier	AC-058B301 EudraCT Number: 2012-000540-10 NCT No.: NCT02425644 Clinical Registry No.: AC-058B301		
Design	Multicentre, randomised, double-blind, parallel group, active-controlled, superiority study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	108 weeks not applicable 30 days	
Hypothesis	Superiority		
Treatments groups	Ponesimod	Ponesimod 20 mg once a day N=567	
	Teriflunomide	Teriflunomide 14 mg once a day N=566	
Endpoints and definitions	Primary endpoint	ARR	ARR up to EOS, defined as the number of confirmed relapses according to the treating neurologist/principal investigator per subject-year.
	Secondary endpoint	12-week CDA	Time to 12-week CDA from baseline to EOS.
	Secondary endpoint	24-week CDA	Time to 24-week CDA from baseline to EOS.
	Secondary endpoint	FSIQ–RMS	Change from baseline to Week 108 in fatigue-related symptoms (FSIQ–RMS)
	Secondary endpoint	CUAL	CUALs from baseline to Week 108
	Exploratory endpoint	Time to first relapse	Time to first confirmed relapse.
	Exploratory endpoint	EDSS	Change from baseline by visit up to Week 108 in EDSS.
Database lock	27 June 2019		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Ponesimod	Teriflunomide
	Number of subjects	567	566
	ARR (mean)	0.202	0.290
	99% CIs 95% CIs	0.165, 0.246 0.173, 0.235	0.244, 0.345 0.254, 0.331
	12-week CDA (% of subjects)	10.1%	12.4%

	24-week CDA (% of subjects)	8.1%	9.9%
	FSIQ–RMS (mean change)	-0.01	3.56
	95% CIs	-1.60, 1.58	1.96, 5.16
	CUALs (mean no./year)	1.405	3.164
	95% CIs	1.215, 1.624	2.757, 3.631
	EDSS (mean change)	0.00	0.13
	95% CIs	-0.07, 0.07	0.07, 0.20
	Time to first relapse (% of subjects up to EOS)	30.3%	39.9%
Effect estimate per comparison	Primary endpoint ARR	Comparison groups	Ponesimod vs. teriflunomide
		RR	0.695
		99% CIs 95% CIs	0.536, 0.902 0.570, 0.848
		P-value (NB regression)	0.0003
	Secondary endpoint 12-week CDA	Comparison groups	Ponesimod vs. teriflunomide
		HR	0.83
		95% CIs	0.58, 1.18
		P-value (stratified log-rank)	0.2939
	Secondary endpoint 24-week CDA	Comparison groups	Ponesimod vs. teriflunomide
		HR	0.84
		95% CI	0.57, 1.24
		P-value (stratified log-rank)	0.3720
	Secondary endpoint FSIQ-RMS	Comparison groups	Ponesimod vs. teriflunomide
		Difference of LS means	-3.57
		95% CI	-5.83, -1.32
		P-value (MMRM)	0.0019
	Secondary endpoint CUALs	Comparison groups	Ponesimod vs. teriflunomide
		RR	0.444
		95% CIs	0.364, 0.542
		P-value (NB regression)	<0.0001
	Exploratory endpoint time to first relapse	Comparison groups	Ponesimod vs. teriflunomide
		HR	0.76
		95% CIs	0.62, 0.93
		P-value (stratified log-rank)	0.0081
	Exploratory endpoint EDSS	Comparison groups	Ponesimod vs. teriflunomide
		LS mean difference	-0.13
		95% CIs	-0.22, -0.04
		P-value (MMRM)	0.0059
Notes	Primary analysis for ARR assumed MAR. Analysis is based on a NB regression model adjusted for stratification factors [EDSS strata (≤3.5,>3.5), DMT in last 2 years prior to randomisation strata (Y,N) and number of relapses (<=1, >=2) in year prior to study.		
Analysis description	**Sensitivity analyses on missing data** **Reference based approach**		

	Primary endpoint ARR	Comparison groups	Ponesimod vs. teriflunomide
		RR	0.717
		95% CIs 99% CIs	0.587, 0.875 0.552, 0.931
		P-value (copy reference)	0.0010
	Primary	Comparison groups	Ponesimod vs. teriflunomide
		RR	0.720
		95% CIs 99% CIs	0.590, 0.879 0.555, 0.936
		P-value (jump to reference)	0.0013

ARR = annualised relapse rate, CDA = confirmed disability accumulation, CIs = Confidence Intervals, CUALs = combined unique active lesions, DMT = disease modifying treatment, EDSS = expanded disability status scale, EOS = end-of-study, FSIQ–RMS = fatigue symptoms and impacts questionnaire – relapsing multiple sclerosis, HR = hazard ratio, LS = least square, MAR = missing at random, MMRM = mixed effects model repeated measurements, NB = negative binomial,

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

Not applicable.

Clinical studies in special populations

Not applicable.

Supportive studies

Study B202

Study B202 is an ongoing, prospective, multicentre, multinational, randomised, DB, multiple-dose, uncontrolled, parallel-group extension study in subjects with RRMS who completed the B201 study.

Subjects who had completed B201 to Week 24 were eligible to enrol into this extension B202 study. The extension study includes a transition period (Day −3 to −1, during which all subjects received their B201 study medication), 3 treatment periods (Treatment Period 1 [TP1], Treatment Period 2 [TP2], and Treatment Period 3 [TP3]), and a posttreatment follow-up period. In TP1, all ponesimod doses were administered, in TP2 10 mg and 20 mg, and in TP3 only the 20 mg dose.

TP1 and TP2 have been completed, and TP3 is currently ongoing. Subjects and investigators remained blinded to study treatment assignment during the core (B201), TP1 and TP2. The main objective of B202 was to investigate the long-term safety and tolerability of ponesimod. The efficacy objectives were to investigate the long-term efficacy of ponesimod and to explore the dose-response relationship of 10, 20, and 40 mg ponesimod on disease control in subjects with RRMS. All objectives were exploratory, and no primary or secondary efficacy endpoints were defined.

Analyses were performed to examine the dose-response (pooled B201/TP1 for 10 mg, 20 mg and 40 mg=AP1; pooled B201/TP1/TP2 for 10 mg and 20 mg=AP2) and long-term efficacy (combined core B201/TP1/TP2/TP3=AP3). Dose-response over long-time treatment can be adequately estimated only for the analysis period AP1, i.e. up to week 96, before any dose switches occurred.

Data is available up to data cut-off date of 31 March 2019. Of the 393 subjects who completed B201, a total of 353 subjects were enrolled into TP1 of B202. In the pooled B201/B202 analysis, the ponesimod

analysis set included a total of 435 subjects who received at least 1 dose of ponesimod during B201 and/or B202. Of these 435 subjects; 139, 145, and 151 subjects were initially randomised to ponesimod 10 mg, 20 mg, and 40 mg, respectively.

As of the cut-off date of the interim analysis (31 March 2019), 42.8% of subjects in the PAS had discontinued study treatment at any time during either B201 or B202. The proportion of subjects discontinuing study treatment was higher in the 40 mg dose group (47.7%) when compared with the 10 mg (41.0%) and 20 mg dose groups (39.3%).

In terms of relapses and disability progression, a clear dose-response was observed, with 40 mg dose yielding the best results. As the examination of efficacy is exploratory, and there is no placebo control, no firm conclusions on efficacy or dose-response in the long-term can be made. However, based on these results, the choice of 20 mg dose is supported, also taking into account the tolerability of the 40 mg dose.

Study B303

Study B301 was followed by study B303, an ongoing prospective, multicentre, open-label, non-comparative, long term extension study, which was conducted to investigate the long-term safety, tolerability, and disease control with ponesimod 20 mg in subjects with RMS.

The planned treatment period was 240 weeks. All efficacy analyses were exploratory and based on three analysis sets: combined (B301+B303), extension (subjects who received at least 1 dose of ponesimod 20 mg in the extension study), and core (core analysis period for the 877 subjects who entered the extension study).

Data is available up to data cut-off date of 31 March 2019. Of the subjects randomised in the core study, 877 (77.4%) subjects (439 on ponesimod 20 mg and 438 on teriflunomide 14 mg) were enrolled in the extension study.

A total of 6.4% of subjects (5.5% in P20 mg/P20 mg and 7.3% in T14 mg/P20 mg) prematurely discontinued treatment during the extension study.

Based on the open-label, explorative efficacy assessments, the ARR observed in the ponesimod group in the pivotal study B301 remained stable during the extension study (0.22, 95% CIs 0.19, 0.25 in the combined analysis set). This also holds true for MRI based key endpoints.

Further, the Kaplan-Meier estimates for 12-week and 24-week CDA remained low: 10.8% and 8.7%, respectively, in study B301 and 14.5% and 12.2%, respectively, in study B303. This may reflect the slow progression of disability in this patient population in general.

2.5.3. Discussion on clinical efficacy

Efficacy of ponesimod in the treatment of RMS was examined in one DB, active-controlled, randomised, parallel-group study B301. In this study, ponesimod 20 mg was administered once daily. Teriflunomide 14 mg administered once daily was the comparator arm.

A supportive dose-response study B201 examined doses of 10 mg, 20 mg and 40 mg vs placebo. In addition, long-term extension studies for both B201 and B301 are currently ongoing.

Design and conduct of clinical studies

Dose-response study B201

This was a prospective, multicentre, randomised, DB, placebo-controlled, parallel-group, dose-finding study, in which efficacy, safety, and tolerability of 3 doses of ponesimod (10, 20, or 40 mg) administered for 24 weeks were investigated in subjects with RRMS. The dose selection for this study was based on both efficacy and safety considerations, based on data from Phase 1 single-ascending and multiple-ascending dose studies. A 30% reduction of peripheral lymphocyte counts which was considered minimum required reduction for selecting the 10 mg dose, may be considered rather small, considering that significant effects have been observed with much higher reductions.

In this study, dose increments were performed in a weekly interval for patients randomised in the 20 mg and 40 mg dose groups. The final up-titration regime selected for the Phase 3 study is different, with small increments up to 10 mg. The applicant performed a cross-over study to examine two up-titration regimes, which supported the choice of a slower up-titration regimen from safety perspective due to first dose effects of ponesimod, resulting in cardiac abnormalities, i.e. HR decrease and AV conduction delays.

The study included patients aged 18 to 55 years with a diagnosis of RRMS according to the revised (2005) McDonald Diagnostic Criteria for MS. Patients were required to have ≥1 documented relapse(s) within 12 months prior to screening or ≥2 documented relapses within 24 months prior to screening or at least 1 Gd+ lesion detected on T1-weighted MRI (central reading) at screening. EDSS score of 0 to 5.5 (inclusive) at screening was required. Both treatment-naïve and patients previously treated with IFN beta-1a, IFN beta-1b, glatiramer acetate, or natalizumab, were eligible to enrol in the study. The study population consisted solely of RRMS patients; this is considered acceptable for a dose-response study.

The primary efficacy endpoint was the cumulative number of new Gd+ lesions per patient on T1-weighted MRI scans at Weeks 12 to 24. The MRI data from weeks 12 to 24 was selected for the calculation of the primary endpoint, due to expected delayed anti-inflammatory action previously seen in fingolimod data. This approach is accepted and was also followed in another recent SP1 modulator dossier. Secondary endpoints included ARR and time to first confirmed relapse. An MRI primary endpoint is accepted for a dose-response study.

The primary statistical analysis was performed using a NB regression model with treatment group as 4 level nominal covariate, which is acceptable.

The applicant also performed E-R modelling based on the results of this study, which is discussed under PD section of this CHMP assessment report.

The study methods are in overall considered acceptable.

Pivotal study B301

Study B301 is a multicentre, randomised, DB, parallel-group, active-controlled, superiority study comparing the efficacy and safety of ponesimod to teriflunomide in subjects with RMS. The treatment period was 108 weeks. The study design as such follows a conventional RMS study for a DMT, with a treatment period of 108 weeks and an active comparator arm, without placebo control.

The applicant thus performed a single pivotal study. This has been discussed in a CHMP AS EMA/H/SA/2170/FU/1/2014/III, EMA/H/SA/2170/4/FU/2/2019/II), where specific advice was given to the applicant concerning, e.g. the level of significance to be applied. A single pivotal study will be assessed in the context of *EMA points to consider an application with 1. Meta-analyses; 2. One pivotal study (CPMP/EWP/2330/99)*. In addition to statistical significance, important aspects to be taken into consideration in the assessment of a single pivotal study are external and internal validity, clinical relevance, data quality and internal consistency.

The inclusion and exclusion criteria are considered acceptable. Both, patients with RRMS and SPMS were included in the study, which has become standard in current MS studies in order to obtain at least some

data in SPMS patients as well when RMS indication is sought. Nevertheless, it is considered that efficacy in terms of relapse rate seen in patients with RRMS can be extrapolated to patients with SPMS, in line with the EMA guideline on clinical investigation of medicinal products for the treatment of Multiple Sclerosis (EMA/CHMP/771815/2011, Rev. 2). Active disease was confirmed with clinical or imaging features, which is acceptable. Treatment-naïve or patients previously treated with DMTs were included in the study, which is acceptable and in line with current treatment practises.

The study included only the 20 mg QD dose of ponesimod. Based on the results of the dose-response study, performed PK/PD modelling exercises and safety data, this is accepted. A gradual up-titration scheme was applied, which is acceptable, as stated earlier.

Teriflunomide is accepted as active control for this study, with an aim to show superiority to an established DMT. Accelerated elimination procedure was applied in the study, due to the very long half-life of teriflunomide. To maintain blinding, the elimination procedure was performed in both treatment arms, which is acceptable.

The primary objective of the study was to determine whether ponesimod is more efficacious than teriflunomide in terms of reducing relapses in subjects with RMS. Secondary objectives were to assess the effect of ponesimod on disability accumulation and on other aspects of MS disease control, and to assess the safety and tolerability of ponesimod in subjects with RMS. The study objectives are acceptable; however, it is noted that the hierarchy of study endpoints does not follow the objectives: the key secondary endpoint defined was fatigue as measured by the symptoms domain of the FSIQ–RMS, not disability progression. Although fatigue is considered a relevant endpoint, disability accumulation is considered more important for the assessment of efficacy. In accordance with the MS guideline, if ARR is the primary endpoint, disability should be the key secondary endpoint. The testing hierarchy was discussed during CHMP SA (EMEA/H/SA/2170/1/2011/III, EMA/H/SA/2170/FU/1/2014/III) even when the study was already ongoing (EMEA/H/SA/2170/1/FU/2/2018/II, EMA/H/SA/2170/4/FU/2/2019/II). The applicant wished to amend the hierarchy by placing disability progression lower in the testing hierarchy. The CHMP advice stressed the importance of disability progression as the key secondary endpoint, expressing concerns on the chosen testing strategy. In the CHMP advice, it was also stated that the 24-week CDA is considered more important than the 12-week CDA; however, it was acknowledged that success in 24-week CDA would be less likely than in the 12-week CDA. The testing hierarchy, as defined in the MS guideline, is followed in this review, thus presenting disability progression data after the primary endpoint ARR. The testing strategy was amended when the study was ongoing, and the applicant was invited to clarify the rationale behind this amendment. The applicant has clarified that the change in the order of the hierarchical testing strategy was performed in a blinded manner and based on results from external studies, to optimise the chance of success for the secondary endpoints. This is accepted.

The primary endpoint was ARR up to EOS, defined as the number of confirmed relapses according to the treating neurologist/principal investigator per subject-year. Relapse definition is in line with previous RMS studies and acceptable. The secondary efficacy variables were change from baseline to Week 108 in fatigue-related symptoms as measured by the symptoms domain of the FSIQ–RMS, CUALs from baseline to Week 108, time to 12-week CDA from baseline to EOS and time to 24-week CDA from baseline to EOS. As already mentioned, disability progression is considered a key secondary endpoint.

The FSIQ-RMS is a PRO developed by the applicant. It is a 20-item PRO measure that was developed by Actelion to evaluate fatigue-related symptoms and the impacts of those symptoms on the lives of people with RMS. The development and validation of the FSIQ-RMS seem adequately performed. The psychometric study in patients with RMS and controls demonstrates good reliability and validity. Concurrent validity was tested against other PRO instruments Modified Fatigue Impact Scale, Patient Global Impression Severity (PGI-S) and RAND 36 Health Survey Version. Correlations were moderate to

high in all comparisons. A correlation of EDSS score and FSIQ-RMS symptoms domain score was also shown. However, as the endpoint has not been included in a clinical study before, its sensitivity to change was not tested before applying the questionnaire in the Phase 3 study. Furthermore, a clinically relevant change was also unknown at the start of the study. These hamper the assessment of results on FSIQ-RMS, as discussed in the results section.

Sample size calculation was based on assumptions derived from TEMSO and TOWER studies, which in hindsight were applicable, and the calculation is accepted.

The analysis sets, primary and secondary endpoint analysis and handling of multiplicity are considered standard and acceptable. Note that the primary null hypothesis will be tested with a two-sided alpha level of 1% for conclusive evidence and 5% for a positive study, which is in line with the CHMP advice in the context of a single pivotal study.

In the chosen estimand and the resulting missing data handling, study discontinuation is seen as a random event, which may not be realistic. However, the applicant provided a sensitivity analysis using reference-based imputation with results similar to the primary analysis, showing the results are robust to the missing data assumption.

Long-term study B202

Study B202 is an ongoing, prospective, multicentre, multinational, randomised, DB, multiple-dose, uncontrolled, parallel-group extension study in subjects with RRMS who completed the B201 study. The extension study includes a transition period (Day −3 to −1, during which all subjects received their B201 study medication), 3 treatment periods (TP1, TP2,TP3), and a posttreatment follow-up period. In TP1, all ponesimod doses were administered; in TP2, 10 mg and 20 mg; and in TP3, only the 20 mg dose.

TP1 and TP2 have been completed, and TP3 is currently ongoing. Subjects and investigators remained blinded to study treatment assignment during the core (B201), TP1 and TP2. Analyses were performed to examine the dose-response (pooled B201/TP1 for 10 mg, 20 mg and 40 mg=AP1; pooled B201/TP1/TP2 for 10 mg and 20 mg=AP2) and long-term efficacy (combined core B201/TP1/TP2/TP3=AP3). Dose-response over long-time treatment can be adequately estimated only for the analysis period AP1, i.e. up to week 96 before any dose switches occurred.

Long-term study B303

Study B301 was followed by study B303, an ongoing prospective, multicentre, open-label, non-comparative, long term extension study, which was conducted to investigate the long-term safety, tolerability, and disease control with ponesimod 20 mg in subjects with RMS.

The planned treatment period was 240 weeks. All efficacy analyses were exploratory and based on three analysis sets: combined (B301+B303), extension (subjects who received at least 1 dose of ponesimod 20 mg in the extension study), and core (core analysis period for the 877 subjects who entered the extension study).

Efficacy data and additional analyses

Dose-response study B201

A statistically significant difference vs. placebo was demonstrated in all three ponesimod groups in the primary endpoint. 40 mg dose does not seem to provide remarkable additional benefit on top of the 20 mg dose in terms of MRI endpoints. The performed dose-response modelling also suggests that the effect of ponesimod plateaus after 20 mg.

However, in ARR, 40 mg dose was the only ponesimod dose separating from placebo. However, the study was not powered to show a statistically significant effect on ARR, and the study duration is likely too short of providing a reliable estimation on ARR. Also, in terms of time to first relapse, the 40 mg dose performed best out of the three ponesimod dose groups. Therefore from an efficacy point of view, both 20 mg and 40 mg doses could have been selected for the pivotal Phase 3 study. From a safety perspective, however, it is accepted that the 40 mg dose was omitted from the Phase 3 study.

Pivotal study B301

A similar proportion of patients discontinued the study prematurely in both treatment groups. In the ponesimod group, more patients discontinued due to tolerability as compared to teriflunomide group. In contrast, more patients in the teriflunomide group discontinued due to lack of efficacy as compared to the ponesimod group.

There were 6 substantial global amendments to the protocol. In amendment 3, a clarification was added concerning the role of the treating neurologist and efficacy assessor in EDSS and FS assessments. The applicant has clarified that this clarification was included as per request of FDA review of the AC-058B302/POINT study protocol and was not triggered by observed deviations in roles of the treating neurologist and efficacy accessor during the study. Moreover, the maximum proportion of patients with a PD related to access to PUD before the clarification was added to the protocol was small i.e. <1%.

All patients included in the study had a least one PD, which is striking. The PDs were balanced between the treatment groups, and as later can be seen, the PP analysis excluding patients with PDs occurring prior to or at randomisation was consistent with the primary analysis. The applicant also provided sensitivity analyses excluding patients with important PDs related to efficacy endpoints and blinding, which demonstrated consistent results with the primary analysis. The noted higher incidence of important PDs in the efficacy/endpoint group is associated with higher relapses rate in the teriflunomide group. The applicant has clarified that this was driven by an imbalance on relapse confirmation PDs. As there were more relapses in the teriflunomide group, the chance of relapse confirmation PDs was also higher. This is accepted. Altogether the applicant has provided a thorough overview and impact assessment of PDs related to efficacy assessments and blinding, thereby addressing the study integrity. The provided clarifications and additional analyses provide adequate assurance of the study integrity and validity of results, and therefore a GCP inspection is not considered required.

The baseline demographic characteristics are usual to MS trials: the majority of patients are female and in mid-thirties. The vast majority of patients included were from study centres in Europe and Russia. The baseline demographic characteristics are balanced between the treatment groups.

The baseline disease characteristics reflect a typical patient with RMS in need of DMT and are largely similar to patient populations included in recently assessed RMS dossiers. Almost half of the patients had previously received a DMT. Only a small number of patients (n=29) with SPMS were included. Approximately 35% of patients were considered to have a highly active disease as per pre-defined criteria. The criteria for the highly active disease are in line with the criteria seen in recent RMS studies. There were some differences between the treatment groups in baseline MRI variables; however, these differences were not reflected in the other baseline disease characteristics and are therefore not considered of concern.

The mean ARR (number of confirmed relapses per year) was 0.202 and 0.290 in the ponesimod 20 mg and teriflunomide 14 mg groups. Ponesimod 20 mg statistically significantly reduced ARR up to EOS by 30.5% compared to teriflunomide 14 mg (ARR ratio: 0.695; 99% CIs 0.536, 0.902; p=0.0003). Thus the study clearly demonstrated the superiority of ponesimod over teriflunomide. Sensitivity analyses were consistent with the primary analysis. However, it is noted that the sensitivity analyses using reference-based imputation of missing data, which could be more realistic than the MAR approach in the

main analysis, show a smaller treatment effect. During the procedure, the applicant has been invited to discuss which missing data handling would provide the most realistic estimate of the effect and should be presented in the product information: the MAR in the main analysis, or the missing data not at random in the reference-based analysis provided as sensitivity analyses. The ARR before discontinuation was lower for ponesimod patients than for teriflunomide. Likewise, data after treatment discontinuation indicated a lower ARR for previous ponesimod use than teriflunomide, so it can be agreed that reference-based imputation may not be the most realistic method of handling missing data. The applicant performed a sensitivity analysis using retrieved dropout imputation, which would then be more realistic. This resulted in a rate ratio of 0.702 (99%CI: 0.538-0.916) which is close to the primary analysis result of 0.695 (0.536, 0.902). Since the results are close together, it is agreed to present the primary analysis assuming missing at random in the SmPC.

There was no statistically significant difference between the treatment groups in disability progression; however, ponesimod was numerically favoured in both 12- and 24-week CDA. The risk for a 12-week CDA event was estimated to be 17% lower with ponesimod 20 mg compared to teriflunomide 14 mg (HR: 0.83; 95% CIs: 0.58, 1.18; p=0.2939). The risk for a 24-week CDA event was estimated to be 16% lower for ponesimod 20 mg compared to teriflunomide 14 mg (HR: 0.84; 95% CIs: 0.57, 1.24; p=0.3720). These observations were confirmed in the supplementary and sensitivity analyses.

The FSIQ-RMS weekly symptoms score remained stable in the ponesimod group while the score increased in the teriflunomide group. As compared to baseline, thus, there was no improvement in the fatigue scores in the ponesimod group. Clinically meaningful change in the FSIQ-RMS was not pre-specified in the study protocol. According to the psychometric analysis based on the data from this pivotal study, a clinically meaningful change at the subject level in the FSIQ-RMS was defined. This was done by anchoring the PGI-S score to the FSIQ-RMS score. A -6.3 change on the FSIQ-RMS was concluded as the meaningful change threshold value at the subject level.

Although it is acknowledged that fatigue is of high relevance to patients with MS and a statistically significant difference to teriflunomide was observed in favour of ponesimod, no clinically relevant improvement in fatigue was demonstrated. The observed mean difference in change in FSIQ-RMS-S between the treatment groups is -3.57 (95% CI -5.83. -1.32), less than -6.3 points, which was determined to be meaningful change threshold at the subject level. The mean change in the ponesimod group from baseline was -0.01.

Based on a patient preference study, the applicant concludes that the observed change of -3.57 in the FSIQ-RMS-S score is equally important to patients as a change of -0.06 in yearly relapse rate, which matches the between-treatment difference in ARR observed in the pivotal study B301 i.e. -0.088. This is a somewhat difficult comparison as while the patient preference study measures absolute changes in the FSIQ-RMS and relapse rate, the comparison is to a between-treatment difference of ponesimod and teriflunomide. A fair comparison would be if the between-treatment comparison would be to placebo.

To further support the clinical relevance of the observed difference in FSIQ-RMS-S between the treatment groups, the applicant presented cumulative distribution curves, which allows examining whether the difference in responders over alternative cut-off point than the meaningful change threshold of -6.3 points is consistent. Based on the provided cumulative distribution curves, the difference between the study arms in subjects with an improvement on the fatigue score is marginal. There is worsening, and the difference between the study arms in the proportion of subjects worsening is around 5% irrespective of whether the cut-off point is +5, + 10 or +15 points. The question remains whether a 5% difference shift in the cumulative distribution curve is of clinical relevance. Moreover, the statistically significant difference in the FSIQ-RMS-S is due to a worsening in the teriflunomide group and not to an improvement in the ponesimod group. In fact, the fatigue score in the ponesimod group remains stable. This appears

logical i.e. the reduction in ARR implies that in the ponesimod group, less new events occur that leads to fatigue. So, the implicit claim that ponesimod has an independent effect on fatigue is not warranted.

It is also noted that other FSIQ-RMS endpoints, i.e. FSIQ-R improvement and FSIQ-RMS impacts domain scores did not show statistically significant differences between the treatment groups. Also, in PGI-S fatigue, the treatment groups did not differ.

Furthermore, it is noted that the baseline FSIQ-RMS, as well as PGI-S scores, indicate that majority of patients had mild fatigue thus little room for improvement.

As the difference between ponesimod and teriflunomide in FSIQ-RMS-S is not considered clinically relevant, the results on FSIQ-RMS-S are not presented in SmPC section 5.1, which should be reserved to results that are statistically compelling and clinically relevant.

The mean CUALs per year were 1.405 for ponesimod 20 mg compared to 3.164 for teriflunomide 14 mg (RR: 0.444; 95% CIs: 0.364, 0.542; p<0.0001). The superiority of ponesimod over teriflunomide was thus clearly demonstrated in this secondary MRI endpoint.

The changes in EDSS score overtime were minimal; nevertheless, the treatment groups separated from week 60 onwards, in favour of ponesimod. The LS mean difference (ponesimod 20 mg − teriflunomide 14 mg) in change from baseline to Week 108 in EDSS score was −0.13 (95% CIs: −0.22, −0.04; p=0.0059).

The key clinical and MRI exploratory endpoints, all consistently show the superiority of ponesimod over teriflunomide. These include e.g. time to first confirmed relapse (p=0.0081), NEDA (NEDA-3, p=0.0004 and NEDA-4, p=0.0026), number of new Gd+ lesions (p<0.0001), number of new / enlarging T2 lesions (p<0.0001) and BVL (p<0.0001). The p values are nominal, as the formal testing procedure was stopped after 12-week CDA.

Only very small changes were observed in the quality of life scores (SF-36) from baseline up to week 108, and there were no notable differences between the treatment groups.

The results of subgroup analyses suggest a rather consistent effect across subgroups. Subgroups with a small number of patients, e.g. SPMS and geographical regions North America and Rest of the World, stand out with wide confidence intervals. It is also notable that in patients with baseline EDSS score >3.5, teriflunomide appears to perform better across all primary and secondary endpoints except CUALs. However there was no significant interaction (p=0.72) between treatment and baseline EDSS (EDSS ≤3.5 and EDSS >3.5) and ARR, CDA and fatigue symptoms, and the efficacy on the CUAL endpoint was the same in EDSS ≤3.5 and pointing at the same biological activity. Therefore the observation is likely a chance finding.

Results on relapses as seen in patients with RRMS can be extrapolated to patients with SPMS. Therefore, the RMS indication would in principle be acceptable.

Long-term study B202

Interim results up to data cut-off of 31 March 2019 are available. Of the 393 subjects who completed B201, a total of 353 subjects were enrolled into TP1 of B202. Of the 310 subjects who completed treatment in TP1, 305 subjects went on to enter TP2. Of the 231 subjects who completed treatment in TP2, a total of 228 subjects went on to enter TP3. 42.8% of subjects in the ponesimod analysis set had discontinued study treatment at any time during either B201 or B202. The proportion of subjects discontinuing study treatment was higher in patients initially randomised to 40 mg (47.7%) when compared with patients initially randomised to 10 mg (41.0%) and 20 mg (39.3%).

In terms of relapses and disability progression, a clear dose-response was observed in AP1, with 40 mg dose yielding the best results. As the examination of efficacy is exploratory, and there is no placebo control, no firm conclusions on efficacy or dose-response in the long-term can be made. However, based on these results, the choice of 20 mg dose is supported, also taking into account the tolerability of the 40 mg dose.

Long-term study B303

Interim results up to data cut-off of 31 March 2019 are available. Of the subjects randomised in the core study, 877 (77.4%) subjects (439 on ponesimod 20 mg and 438 on teriflunomide 14 mg) were enrolled in the extension study. A total of 6.4% of subjects (5.5% in P20 mg/P20 mg and 7.3% in T14 mg/P20 mg) prematurely discontinued treatment during the extension study.

Based on the open-label, explorative efficacy assessments, the ARR observed in the ponesimod group in the pivotal study B301 remained stable during the extension study (0.22, 95% CI 0.19, 0.25 in the combined analysis set). This also holds true for MRI based key endpoints.

Further, the Kaplan-Meier estimates for 12-week and 24-week CDA remained low: 10.8% and 8.7%, respectively, in study B301 and 14.5% and 12.2%, respectively, in study B303. This may reflect the slow progression of disability in this patient population in general.

Additional analyses

Additionally, to compare ponesimod 20 mg with placebo and with DMTs, the sponsor has conducted pre-planned analyses using data from study B301 and those of published studies of other DMTs for MS. These include a MAIC to the TEMSO study comparing teriflunomide to placebo and a MBMA.

No firm conclusion on ponesimod performance against placebo or its position in the array of DMTs can be made due to common drawbacks of indirect comparisons. However, this is not of concern as the pivotal study performed according to state-of-art has demonstrated superiority to an approved DMT.

2.5.4. Conclusions on the clinical efficacy

Efficacy of ponesimod in the treatment of RMS was examined in one pivotal study, supported by a dose-response study and the long-term extension studies of both of these studies. The design of the studies follows conventional MS studies. The clinical programme is considered adequate, and the requirements for a single pivotal trial are met. Study integrity has been confirmed and a GCP inspection is not considered required.

Ponesimod 20 mg demonstrated clear superiority to teriflunomide in relapses in the pivotal study, with a p-value of <0.0003 with 1% two-sided alpha. This was supported across key MRI endpoints. There was no statistically significant difference between the treatment groups in disability progression. The applicant opted to apply the fatigue score FSIQ-RMS as the key secondary endpoint; however, no clinically relevant changes in this endpoint were observed, which would support presenting the results in the SmPC. Other relevant clinical endpoints, such as NEDA also demonstrated the superiority of ponesimod over teriflunomide.

A limited number of patients with SPMS was included. However, as efficacy in relapses can be extrapolated from RRMS to SPMS, the indication RMS would in principle be acceptable.

2.6. Clinical safety

Patient exposure

As of the cut-off dates March 2019, 2205 subjects have been exposed to ponesimod, including 1438 subjects exposed to ponesimod monotherapy in the MS clinical programme, with long-term safety information of up to 9 years of continuous treatment available (more than 8 years for more than 200 MS subjects).

Studies in support of RMS consist of 16 phase 1 studies, 2 phase 2 studies (B201, B202) and 1 phase 3 study (B301). The extension studies are ongoing at the time of filing, and interim analyses were performed including all data up to and including the cut-off dates (31 March 2019 for AC-058B202 and 30 May 2019 for AC-058B303).

Safety data from Phase 2 and 3 studies in MS patients were pooled in 3 different analysis periods (Table 15 and Figure 15) to:

- compare the short-term safety of 3 ponesimod doses (10 mg, 20 mg, and 40 mg) with placebo and teriflunomide (6-month pool).
- compare the medium-term safety of 3 ponesimod doses versus teriflunomide (2-year pool).
- characterise the long-term safety of ponesimod (long-term pool).

The applicant provided not only the pooled analysis as indicated above, but for each safety topic, the following results were also presented:

- the long-term pool analysis (focusing on the 20 mg dose) to show the safety profile of ponesimod with the longest treatment duration and highest exposure and to assess whether safety events were reversible based on follow-up data collected upon treatment discontinuation without interference from treatment/dose switching;
- the pivotal Phase 3 study (B301) for comparison between ponesimod at the label recommended maintenance dose (20 mg) with the active comparator teriflunomide (14 mg);
- the Phase 2 study (B201) for a 6-month dose comparison between ponesimod treatment with placebo and dose-response assessment;
- AP1 of Studies B201/B202 (median exposure of 2 years) for dose-response assessment (ie, before ponesimod dose switching occurred).

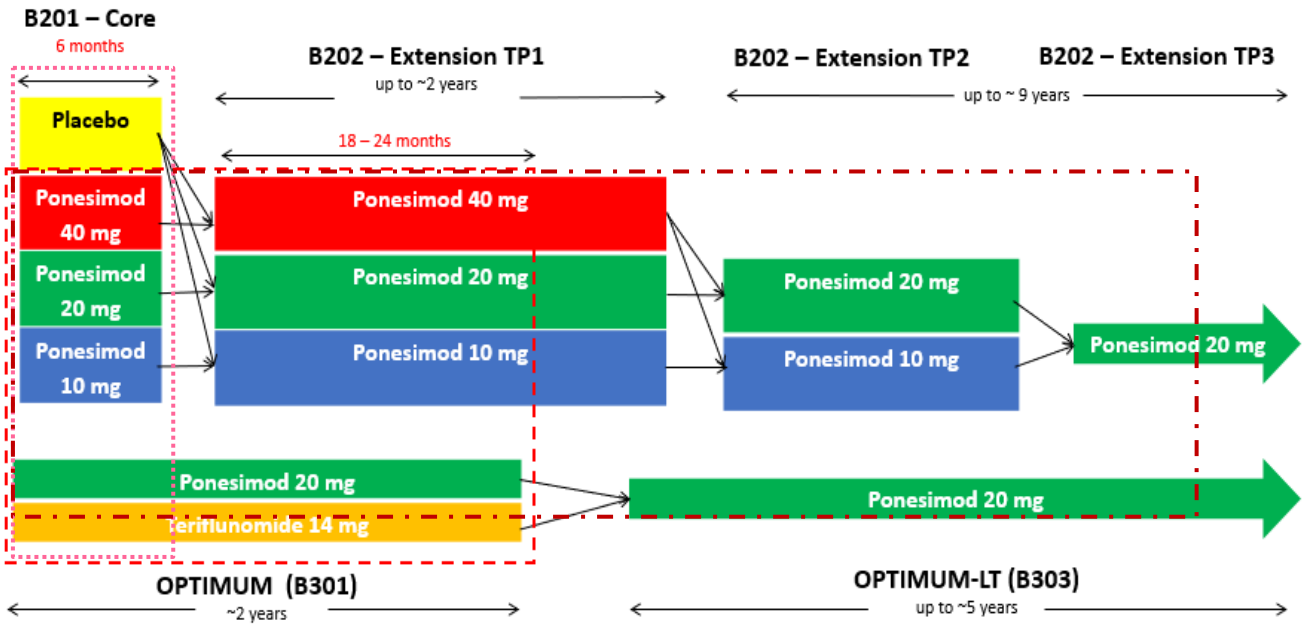
In the long-term pool, the majority of ponesimod-treated subjects were white (97.2%), female (65.9%), and <40 years of age (58.1%). The mean age was 37.4 years (range: 18–58 years). Most of the subjects were enrolled at centres in EU + UK + Switzerland (52.3%), followed by Europe Non-EU + Russia (36.4%), North America (9.0%), and the rest of the world (2.3%).

The demographic characteristics of ponesimod-treated subjects in the 6-month pool and 2-year pool were similar to those in the long-term pool.

Table 15: Summary of Composition of Safety Data Pools

Studies Included and Treatment Duration	Number of Subjects included (per Study and Treatment Group)	Comparison
6-month pool		
B201 (24 weeks)	Placebo, N=121 Ponesimod 10 mg, N=108 Ponesimod 20 mg, N=114 Ponesimod 40 mg, N=119	6-month comparison of safety for ponesimod 10 mg, 20 mg, and 40 mg versus placebo and teriflunomide 14 mg
B301 (first 24 weeks)	Ponesimod 20 mg, N=565 Teriflunomide 14 mg, N=566	
2-year pool		
B201 (24 weeks, only subjects from the ponesimod groups) + B202 (first 84 weeks for subjects treated with ponesimod or first 108 weeks for subjects treated with placebo in B201)	Ponesimod 10 mg, N=139 Ponesimod 20 mg, N=145 Ponesimod 40 mg, N=151	2-year comparison of safety for ponesimod 10 mg, 20 mg, and 40 mg versus teriflunomide 14 mg
B301 (108 weeks)	Ponesimod 20 mg, N=565 Teriflunomide 14 mg, N=566	
Long-term pool		
B201 (24 weeks) + B202 (to cutoff date)	Ponesimod 10 mg, N=139 Ponesimod 20 mg, N=145 Ponesimod 40 mg, N=151	Long-term assessment of safety for ponesimod 10 mg, 20 mg, and 40 mg
B301 (108 weeks, only subjects from the ponesimod 20 mg group) + B303 (to cutoff date)	Ponesimod 20 mg, N=1003	

Figure 15: Composition of safety analysis pools



Adverse events

Table 16 includes treatment-emergent adverse events (TEAEs) by frequency for the pool analysis for 2 months, 2 years and long-term exposure. Subjects in the 6-month and 2-year pool are summarised under their first randomised treatment group.

Table 16: Overview of TEAEs (Frequency); Analysis Set: 6 Month Pool, 2 Years Pool and Long-term Pool Analysis Set

6-month pool					
Subjects with at least one	**Placebo N=121**	**Ponesimod 10mg N=108**	**Ponesimod 20mg N=679**	**Ponesimod 40mg N=119**	**Teriflunomide 14mg N=566**
AE	91 (75.2)	84 (77.8)	459 (67.6)	88 (73.9)	351 (62.0)
Severe AE	9 (7.4)	10 (9.3)	25 (3.7)	6 (5.0)	15 (2.5)
AE leading to discontinuation	4 (3.3)	12 (11.1)	38 (5.6)	16 (13.4)	22 (3.9)
SAE	7 (5.8)	7 (6.5)	20 (2.9)	3 (2.5)	17 (3.0)
Fatal AE	0	0	0	0	1 (0.2)

2year pool				
Subjects with at least one	**Ponesimod 10mg**	**Ponesimod 20mg**	**Ponesimod 40mg**	**Teriflunomide 14mg**
AE	125 (89.9)	624 (87.9)	139 (92.1)	497 (87.8)
Severe AE	18 (12.9)	52 (7.3)	13 (8.6)	26 (4.6)
AE leading to discontinuation	17 (12.2)	61 (8.6)	27 (17.9)	34 (6.0)
SAE	14 (10.1)	64 (9.0)	7 (4.6)	46 (8.1)
Fatal AE	0	0	0	2 (0.4)

Long term pool	
Subjects with at least one	**Ponesimod 20mg**
AE	944 (82.2)
Severe AE	91 (7.9)
AE leading to discontinuation	97 (8.4)
SAE	104 (9.1)
Fatal AE	1 (0.1)

AE = adverse event, SAE = serious AE. Subjects in 6-month and 2-year pool are summarised under their first randomised treatment group.

The incidences of TEAEs in Study B301 by System Organ Classes (SOC) are listed in Table 17 and the most commonly reported TEAEs by preferred term (PT) are presented in Table 18. The most commonly reported TEAEs (≥10% of subjects) in both treatment groups were increased ALT, nasopharyngitis, headache, and upper respiratory tract infection.

Table 17: TEAEs by Primary System Organ Class; Analysis Set: B301 Safety Set

System Organ Class	Ponesimod 20 mg N=565		Teriflunomide 14 mg N=566	
	n	(%)	n	(%)
Subjects with at least one event	502	(88.8)	499	(88.2)
Infections and infestations	306	(54.2)	295	(52.1)
Investigations	187	(33.1)	134	(23.7)
Nervous system disorders	173	(30.6)	149	(26.3)
Gastrointestinal disorders	142	(25.1)	174	(30.7)
Musculoskeletal and connective tissue disorders	112	(19.8)	101	(17.8)
General disorders and administration site conditions	85	(15.0)	92	(16.3)
Respiratory, thoracic and mediastinal disorders	76	(13.5)	60	(10.6)
Skin and subcutaneous tissue disorders	72	(12.7)	145	(25.6)
Psychiatric disorders	65	(11.5)	81	(14.3)
Eye disorders	64	(11.3)	57	(10.1)
Vascular disorders	60	(10.6)	58	(10.2)
Injury, poisoning and procedural complications	55	(9.7)	50	(8.8)
Metabolism and nutrition disorders	47	(8.3)	40	(7.1)
Cardiac disorders	36	(6.4)	28	(4.9)
Blood and lymphatic system disorders	32	(5.7)	34	(6.0)
Renal and urinary disorders	28	(5.0)	30	(5.3)
Reproductive system and breast disorders	28	(5.0)	34	(6.0)
Surgical and medical procedures	25	(4.4)	12	(2.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	23	(4.1)	24	(4.2)
Ear and labyrinth disorders	22	(3.9)	14	(2.5)
Hepatobiliary disorders	14	(2.5)	20	(3.5)
Endocrine disorders	10	(1.8)	6	(1.1)
Congenital, familial and genetic disorders	4	(0.7)	4	(0.7)
Pregnancy, puerperium and perinatal conditions	4	(0.7)	3	(0.5)
Immune system disorders	3	(0.5)	9	(1.6)
Social circumstances	2	(0.4)	1	(0.2)

SOC are based on MedDRA version 21.0. SOC and sorted by descending order of frequency in the ponesimod 20 mg arm.

Table 18: TEAEs Occurring in at Least 5% of Subjects in Any Treatment Group, by PT; Analysis Set: B301 Safety Set

Preferred Term	Ponesimod 20 mg N=565		Teriflunomide 14 mg N=566	
	n	(%)	n	(%)
Alanine aminotransferase increased	110	(19.5)	53	(9.4)
Nasopharyngitis	109	(19.3)	95	(16.8)
Headache	65	(11.5)	72	(12.7)
Upper respiratory tract infection	60	(10.6)	59	(10.4)
Hypertension	45	(8.0)	44	(7.8)
Nausea	43	(7.6)	47	(8.3)
Aspartate aminotransferase increased	36	(6.4)	20	(3.5)
Fatigue	34	(6.0)	37	(6.5)
Back pain	33	(5.8)	38	(6.7)
Urinary tract infection	32	(5.7)	29	(5.1)
Dyspnoea	30	(5.3)	7	(1.2)
Depression	21	(3.7)	29	(5.1)
Diarrhoea	20	(3.5)	44	(7.8)
Alopecia	18	(3.2)	72	(12.7)

PTs are based on MedDRA version 21.0 and sorted by descending order of frequency in the ponesimod arm.
Unrounded percentages were used to filter frequent PTs.

The most common reported AEs are presented listed in Table 19 by SOC and PT for the long-term treatment pool. The AEs reported for the 10mg, and 40mg dose are also included to allow assessment of dose-related AEs.

Table 19: TEAEs by primary system organ class and preferred term (frequency) Analysis set: Long-term pool analysis set *

System organ class	Ponesimod 10 mg N = 139 n (%)	Ponesimod 20 mg N = 1148 n (%)	Ponesimod 40 mg N = 151 n (%)
Subjects with at least one event	132 (95.0)	944 (82.2)	148 (98.0)
Infections and infestations	98 (70.5)	554 (48.3)	107 (70.9)
Nasopharyngitis	43 (30.9)	200 (17.4)	43 (28.5)
Upper respiratory tract infection	26 (18.7)	113 (9.8)	38 (25.2)
Urinary tract infection	18 (12.9)	67 (5.8)	21 (13.9)
Bronchitis	21 (15.1)	56 (4.9)	20 (13.2)
Influenza	20 (14.4)	52 (4.5)	20 (13.2)
Rhinitis	14 (10.1)	37 (3.2)	2 (1.3)
Respiratory, thoracic and mediastinal disorders	46 (33.1)	174 (15.2)	74 (49.0)
Dyspnoea	10 (7.2)	52 (4.5)	22 (14.6)
Cough	11 (7.9)	36 (3.1)	27 (17.9)
Oropharyngeal pain	10 (7.2)	22 (1.9)	10 (6.6)
Obstructive airways disorder	7 (5.0)	19 (1.7)	8 (5.3)
Nervous system disorders	78 (56.1)	307 (26.7)	75 (49.7)
Headache	36 (25.9)	125 (10.9)	38 (25.2)
Dizziness	18 (12.9)	53 (4.6)	18 (11.9)
Paraesthesia	7 (5.0)	27 (2.4)	5 (3.3)
Migraine	9 (6.5)	19 (1.7)	11 (7.3)
Investigations	52 (37.4)	350 (30.5)	64 (42.4)
Alanine aminotransferase increased	16 (11.5)	188 (16.4)	18 (11.9)
Aspartate aminotransferase increased	6 (4.3)	58 (5.1)	7 (4.6)

System organ class	Ponesimod 10 mg N = 139 n (%)	Ponesimod 20 mg N = 1148 n (%)	Ponesimod 40 mg N = 151 n (%)
Forced expiratory volume decreased	9 (6.5)	16 (1.4)	16 (10.6)
Blood cholesterol increased	7 (5.0)	12 (1.0)	6 (4.0)
Pulmonary function test decreased	4 (2.9)	4 (0.3)	8 (5.3)
General disorders and administration site conditions	30 (21.6)	180 (15.7)	56 (37.1)
Fatigue	13 (9.4)	76 (6.6)	14 (9.3)
Oedema peripheral	1 (0.7)	19 (1.7)	16 (10.6)
Musculoskeletal and connective tissue disorders	53 (38.1)	223 (19.4)	51 (33.8)
Back pain	15 (10.8)	75 (6.5)	21 (13.9)
Arthralgia	14 (10.1)	43 (3.7)	11 (7.3)
Musculoskeletal pain	8 (5.8)	17 (1.5)	5 (3.3)
Muscle spasms	7 (5.0)	15 (1.3)	8 (5.3)
Gastrointestinal disorders	45 (32.4)	245 (21.3)	52 (34.4)
Nausea	4 (2.9)	60 (5.2)	9 (6.0)
Diarrhoea	11 (7.9)	41 (3.6)	9 (6.0)
Abdominal pain upper	5 (3.6)	27 (2.4)	9 (6.0)
Vomiting	7 (5.0)	16 (1.4)	4 (2.6)
Psychiatric disorders	32 (23.0)	141 (12.3)	30 (19.9)
Depression	6 (4.3)	40 (3.5)	9 (6.0)
Insomnia	9 (6.5)	38 (3.3)	10 (6.6)
Anxiety	7 (5.0)	37 (3.2)	6 (4.0)
Injury, poisoning and procedural complications	48 (34.5)	119 (10.4)	31 (20.5)
Contusion	9 (6.5)	15 (1.3)	8 (5.3)
Eye disorders	30 (21.6)	132 (11.5)	31 (20.5)
Eye pain	7 (5.0)	9 (0.8)	3 (2.0)
Vascular disorders	22 (15.8)	105 (9.1)	22 (14.6)
Hypertension	14 (10.1)	79 (6.9)	14 (9.3)
Metabolism and nutrition disorders	25 (18.0)	104 (9.1)	20 (13.2)
Hypercholesterolemia	12(8.6)	37 (3.2)	10 (6.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	21 (15.1)	61 (5.3)	21 (13.9)
Melanocytic naevus	7 (5.0)	15 (1.3)	7 (4.6)
Blood and lymphatic system disorders	17 (12.2)	150 (13.1)	18 (11.9)
Skin and subcutaneous tissue disorders	37 (26.6)	139 (12.1)	30 (19.9)
Cardiac disorders	22 (15.8)	68 (5.9)	12 (7.9)
Reproductive system and breast disorders	23 (16.5)	68 (5.9)	17 (11.3)

*Table amended by the assessor to include the PT frequency which were reported ≥5% of subjects
SOCs are based on MedDRA version 21.0 and sorted by descending order of frequency from highest to lowest dose of ponesimod.
Subjects remain on their initial randomised dose of ponesimod from the beginning to the end of this period.

An updated safety report was submitted with the cut-off date March 2020. The reported AEs were generally in line with the events reported with the cut-off date March 2019. In the sections below the pattern and nature of the majority of the adverse events of special interests (AESI) were consistent with the original safety report. Only relevant updates are included.

Serious adverse event/deaths/other significant events

Serious adverse events

In the long-term pool, the incidences of SAEs by SOC are listed in Table 20 while rare, the most commonly reported SAEs by PT in the ponesimod 20 mg group were appendicitis (6 subjects, 0.5%), abdominal pain (4 subjects, 0.3%), MS relapse, invasive ductal breast carcinoma, uterine leiomyoma, and cholelithiasis (3 subjects, 0.3% each).

Table 20: Serious TEAEs by Primary System Organ Class (Frequency); Analysis Set: Long-term Pool Analysis Set

System organ class	Ponesimod 10 mg N = 139 n (%)	Ponesimod 20 mg N = 1148 n (%)	Ponesimod 40 mg N = 151 n (%)
Subjects with at least one event	27 (19.1)	104 (9.1)	23 (15.2)
Infections and infestations	1 (0.7)	21 (1.8)	8 (5.3)
Nervous system disorders	4 (2.9)	16 (1.4)	3 (2.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (2.9)	14 (1.2)	3 (2.0)
Gastrointestinal disorders	1 (0.7)	11 (1.0)	1 (0.7)
Surgical and medical procedures	1 (0.7)	10 (0.9)	1 (0.7)
Hepatobiliary disorders	1 (0.7)	8 (0.7)	0
Reproductive system and breast disorders	2 (1.4)	7 (0.6)	4 (2.6)
Injury, poisoning and procedural complications	6 (4.3)	7 (0.6)	2 (1.3)
Musculoskeletal and connective tissue disorders	2 (1.4)	5 (0.4)	0
Renal and urinary disorders	0	4 (0.3)	0
Eye disorders	2 (1.4)	3 (0.3)	3 (2.0)
Respiratory, thoracic and mediastinal disorders	0	3 (0.3)	2 (1.3)
General disorders and administration site conditions	1 (0.7)	3 (0.3)	1 (0.7)
Vascular disorders	0	3 (0.3)	1 (0.7)
Investigations	2 (1.4)	3 (0.3)	0
Psychiatric disorders	0	3 (0.3)	0
Blood and lymphatic system disorders	0	2 (0.2)	0
Metabolism and nutrition disorders	0	2 (0.2)	0
Cardiac disorders	4 (2.9)	1 (0.1)	0

Subjects are summarised under their first randomised/allocated ponesimod dose group.
SOCs are based on MedDRA version 21.0.

In Study B201, the incidence of serious TEAEs was similar between ponesimod-treated (17 of 341, 5.0%) subjects and placebo-treated subjects (4.1%). Most SAEs were reported in individual subjects, except macular oedema, which was reported in 2 subjects in the ponesimod 20 mg group, and AV block second degree, which was reported in 3 subjects on Day 1 after taking the first dose of ponesimod (10 mg).

Studies B201/B202 during AP1, 14 (10.1%) subjects in the 10 mg dose group, 15 (10.3%) subjects in the 20 mg dose group, and 7 (4.6%) subjects in the 40 mg dose group had at least one serious TEAE, corresponding to an exposure-adjusted incidence rate of 7.1, 6.8, and 3.9 per 100 subject years, respectively. Most SAE PTs were reported in individual subjects, and no clear dose-related trends were observed in the reporting of individual subjects. By SOC, there were more subjects in the 40 mg dose group who had an SAE in the SOC of Infections and infestations (5 [3.3%] subjects, compared to 0

subjects in the 10 mg dose group and 2 [1.4%] subjects in the 20 mg dose group). Drug-related SAEs (i.e., SAEs that were judged by the investigator to have a reasonable possibility of causal relationship to the use of the study drug) were observed in 8 (5.8%), 6 (4.1%), and 3 (2.0%) subjects in the 10 mg, 20 mg, and 40 mg dose groups, respectively.

In study B301, the most commonly reported SAEs in both treatment groups were in the SOCs of Nervous system disorders (1.6% ponesimod 20 mg versus 1.1% teriflunomide 14 mg) and Infections and infestations (1.2% ponesimod 20 mg versus 0.7% teriflunomide 14 mg). Serious AEs occurring in >2 subjects were appendicitis (n=3 (0.5%) in ponesimod 20 mg group versus 0 in teriflunomide group), abdominal pain (n=3 (0.5%) in 20 mg ponesimod group vs 0 in teriflunomide group) and cholelithiasis (n=3 (0.5%) in teriflunomide 14 mg group vs 0 in ponesimod 20 mg group).

In the AC-058B303 extension study, 24 new cases of SAEs were reported in the updated safety report with cut-off date March 2020. Seventeen resolved without sequelae, 3 solved with sequela and 4 are not resolved/currently ongoing. These include invasive breast carcinoma, ligament sprain, epilepsy and chronic bronchitis.

An additional 7 new cases of serious adverse events were reported in 6 subjects in the safety database. These concerned diverticulitis, mitral valve prolapse and duodenal ulcer haemorrhage, hypertensive crisis, headache, ligament sprain, metrorrhagia, pheochromocytoma. All but mitral valve prolapse resolved without sequelae.

Deaths

A total of 3 deaths have been reported in Phase 2 and 3 MS studies, 1 in the ponesimod 20 mg group and 2 in the teriflunomide 14 mg group. Two additional deaths were reported in non-MS studies (Studies 112 and A201). None of the AEs leading to death in any of the studies was assessed by the investigator as related to study treatment. No new deaths were reported in the updated safety report with the cut-off date March 2020.

Safety of special interest

Immunological effect

In the long-term pool ponesimod treatment resulted in a rapid decrease in the estimated mean lymphocyte count (based on a MMRM analysis) from baseline (absolute value=1.87×10^9, n=1146) to Week 4 (reduced by 59.12% in ponesimod 20 mg group to 0.75×10^9, n=1103), which stayed relatively stable through Week 468 (reduced by 52.79% to 0.84×10^9, n=45)

For subjects in the ponesimod 20 mg group, the absolute mean lymphocyte count was 1.849×10^9/L (n=1146), 0.735×10^9/L (n=1135), 1.488×10^9/L (n=75), and 1.722×10^9/L (n=99) at baseline, the last on-treatment, FU (follow-up) Day 7, and FU Day 15, respectively, indicating a rapid reversal of lymphocyte count upon treatment discontinuation.

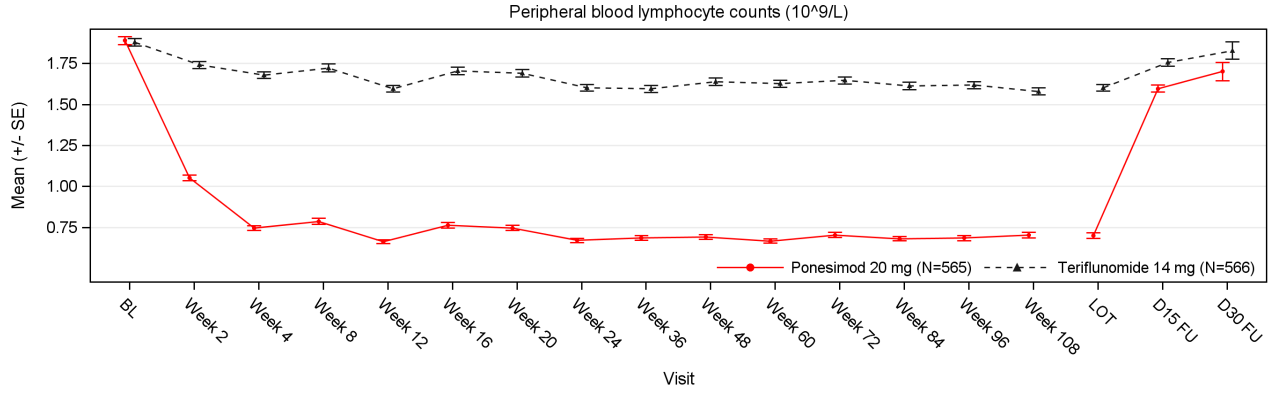
In Study B301, the rapid decrease in lymphocyte count from baseline to Week 2 and Week 4 in the ponesimod 20 mg group (mean % change from baseline of -42.34% and -59.15%, respectively) compared to the teriflunomide 14 mg group (-5.21% and -8.45%, respectively) is also shown in Figure 16 From Week 12 to Week 108, mean lymphocyte count in the ponesimod 20 mg group remained stable (Figure 16). The mean % decrease from baseline in lymphocyte count at last on-treatment timepoint was -61.17% in the ponesimod 20 mg group, compared to -12.49% in the teriflunomide 14 mg group.

Upon discontinuation of ponesimod treatment, the % of subjects with lymphocyte counts above $0.8x10^9$/L was 37.9% (11/29), 84.6% (11/13) and 98.5% (202/205) in study B301, by FU Day 2, FU

day 5 and FU day 15, respectively. Similar results were seen in study B301, with a lymphocyte counts above 0.8x10^9/L for 98.8% by FU Day 15 (n=484, both B201 and B301).

The mean % decrease from baseline in lymphocyte count was -7.38% at FU Day 15 and -4.39% at FU Day 30. These results indicated that the decrease in lymphocyte count was reversible.

Figure 16: Mean (plus/minus SE) Peripheral Blood Lymphocyte Count by Visit; Analysis Set: B301 Safety Set



Number of Subjects																		
Ponesimod 20 mg	563	550	540	403	533	420	433	520	504	497	495	487	476	463	464	560	484	101
Teriflunomide 14 mg	566	554	551	429	541	448	443	535	523	503	492	490	481	474	466	564	495	100

BL: Baseline (last value prior first study drug intake), LOT: Last on treatment, D15 FU: Day-15 Follow-up, D30 FU: Day-30 Follow-up.
Only central laboratory results were included. Except for baseline and follow-up, only treatment-emergent results were included.

Infection

Ponesimod reduces the number of circulating lymphocytes, which may increase the risk of infections.

The overall rate of infections was comparable between subjects receiving ponesimod 20 mg and those receiving teriflunomide 14 mg (54.2% vs 52.1%, respectively).

The most commonly reported TEAEs were nasopharyngitis (17.4%), upper respiratory tract infection (9.8%), and urinary tract infection (5.8%). No cases of PML, cryptococcal meningitis, or any other opportunistic infections with fatal outcome were reported in any ponesimod dose group.

Serious or severe AEs in the SOC of Infections and infestations are identified as infection AESIs. A total of 42 (out of 1438) ponesimod-treated subjects (25 [2.2%] in the ponesimod 20 mg group) reported an infection AESI (Table 21). TEAEs by PT reported in more than 1 subject in the ponesimod 20 mg group included appendicitis (6 subjects, 0.5%, all serious), urinary tract infection (2 subjects, 0.2%, both serious), and pneumonia (2 subjects, 0.2%, 1 serious).

No case of fatal infections has been reported in ponesimod-treated subjects. In the ponesimod 20 mg group, 0.2% subjects had infection AESIs that led to treatment discontinuation, and 1.8% subjects had serious infection AESIs.

Among the 25 (2.2%) subjects in the ponesimod 20 mg group who had infection AESIs, 31 events were reported, indicating that only a few subjects had recurrent events. The event rate per 100 subject-years was 0.6, 1.2, and 2.3 in the ponesimod 10 mg, 20 mg, and 40 mg groups, respectively, suggesting dose-dependency of the incidence of infection AESIs.

Table 21: Treatment-emergent Infection AESIs by PT (Frequency); Analysis Set: Long-term Pool Analysis Set

Preferred term	Ponesimod 10 mg N = 139 n (%)	Ponesimod 20 mg N = 1148 n (%)	Ponesimod 40 mg N = 151 n (%)
Subjects with at least one event	4 (2.9)	25 (2.2)	13 (8.6)
Appendicitis	0	6 (0.5)	1 (0.7)
Pneumonia	0	2 (0.2)	2 (1.3)
Urinary tract infection	0	2 (0.2)	0
Influenza	0	1 (0.1)	2 (1.3)
Nasopharyngitis	0	1 (0.1)	2 (1.3)
Cellulitis	1 (0.7)	1 (0.1)	1 (0.7)
Upper respiratory tract infection	0	1 (0.1)	1 (0.7)
Gastroenteritis	1 (0.7)	1 (0.1)	0
Herpes zoster	1 (0.7)	1 (0.1)	0
Abdominal infection	0	1 (0.1)	0
Acute sinusitis	0	1 (0.1)	0
Chronic hepatitis C	0	1 (0.1)	0
Furuncle	0	1 (0.1)	0
Gastrointestinal infection	0	1 (0.1)	0
Hepatitis B	0	1 (0.1)	0
Infectious colitis	0	1 (0.1)	0
Liver abscess	0	1 (0.1)	0
Meningitis viral	0	1 (0.1)	0
Peritonitis	0	1 (0.1)	0
Pilonidal cyst	0	1 (0.1)	0
Pyelonephritis acute	0	1 (0.1)	0
Respiratory tract infection viral	0	1 (0.1)	0
Staphylococcal abscess	0	1 (0.1)	0
Wound infection	0	1 (0.1)	0
Gastroenteritis viral	0	0	2 (1.3)
Anal abscess	0	0	1 (0.7)
Bronchitis	0	0	1 (0.7)
Dental gangrene	0	0	1 (0.7)
Sinobronchitis	0	0	1 (0.7)
Corneal infection	1 (0.7)	0	0
Pharyngitis	1 (0.7)	0	0

Subjects are summarised under their first randomised/allocated ponesimod dose group.
PT are based on MedDRA version 21.0.PTs and sorted by descending order of frequency in the ponesimod 20 mg arm. If the frequencies of SOCs are the same, sorting is performed by descending order of frequency in the remaining arms within the following order: ponesimod 40 mg, ponesimod 10 mg.

Herpetic Infection

The incidence of herpetic infection TEAEs (including oral herpes) in ponesimod 20 mg-treated subjects was not dose-dependent, and not higher than either placebo- or teriflunomide 14 mg-treated subjects.

In the long-term pool, 4.4% of subjects in the ponesimod 20 mg group had a herpetic infection AESI. The most commonly (>1% subject) reported PTs in the ponesimod 20 mg group were oral herpes (2.4%) and herpes zoster (1.7%). Ophthalmic herpes zoster was reported in 1 subject.

Skin Malignancy

In the long-term pool, 0.6% of subjects in the ponesimod 20 mg group had a skin malignancy AESI. The only PTs that were reported in more than 1 subject in the ponesimod 20 mg group were basal cell carcinoma (4 subjects, 0.3%) and skin neoplasm excision (2 subjects, 0.2%).

Basal cell carcinoma was reported in 7 subjects 1.9 to 8.0 years after initiation of ponesimod treatment in MS studies. Two subjects on ponesimod 20 mg underwent removal of dysplastic naevus. While dysplastic naevus is not a PT of skin malignancy AESI, the reported term "dysplastic naevus excision" was coded to "skin neoplasm excision", and thus counted as a skin malignancy AESI.

Malignant melanoma was reported 1.9 years after initiation of ponesimod treatment in a subject with a medical history of benign and malignant skin lesions. The event rate per 100 subject years is 0.348 in the ponesimod 20 mg group.

Non-skin malignancy

In the long-term pool, 10 (0.7%) of 1438 subjects in the total ponesimod group (including 5 in the ponesimod 20 mg group) had a non-skin malignancy AESI. The only PT that was reported in more than 1 subject in the ponesimod 20 mg group was invasive ductal breast carcinoma (3 subjects, 0.3%).

Breast cancer was reported in 6 female subjects (ages ranging 40-60 years) 3 years (median) (range 4 months – 8.3 years) after initiation of ponesimod 10mg (3 cases), 20mg (2 cases) or 40mg (1 case).

Cervical carcinoma was reported in 2 subjects (one case of adenocarcinoma and another case of squamous cell carcinoma in two females in their 40's treated with ponesimod 10mg and 20mg for 1-4 years.

B-Cell lymphoma was reported in 1 subject (age ranging 55-65) positive for Epstein-Barr virus prior to study entry and treated with ponesimod over 2-3 years.

One event of esophageal adenocarcinoma was reported in MS Studies.

Five (0.4%) subjects in the ponesimod 20 mg group had a serious non-skin malignancy AESI. Three (0.3%) subjects in the ponesimod 20 mg group had a non-skin malignancy AESIs that led to treatment discontinuation. The event rate per 100 subject years is 0.19 in the ponesimod 20 mg group.

Cardiovascular effects

First dose effect

Treatment-emergent AEs observed on the first day of ponesimod dosing in a total of 74 (17.0%) subjects. The most common TEAEs by PT were dizziness (n=22 (5.1%), headache (n=15 (3.4%), fatigue (n=10 (2.3%), bradycardia (n=8 (1.8%), vertigo (n=6 (1.4), nausea (n=5 (1.1%), and first degree AV block (n=5 (1.1%). All other PTs reported on Day 1 were observed in <1% of subjects.

Most TEAEs in this AESI category were mild or moderate and occurred on a single occasion. There were 8 subjects who had a TEAE in this AESI category that was recorded as serious and/or led to discontinuation of study treatment. All these events occurred on Day 1 and resolved without sequelae following discontinuation of ponesimod treatment (with the exception first degree AV block in one subject, which was unresolved).

Events of syncope/presyncope were reported by 6 subjects, none of them occurred on Day 1. Overall, syncopic events were not associated with ponesimod treatment initiation or reinitiation

Serious TEAEs

Serious adverse events occurring on the first day of dosing (Day 1, ie, following the first dose of ponesimod [10 mg]) were reported in 5 (1.1%) subjects. Of the 5 SAEs reported on Day 1, 4 led to premature discontinuation: 3 subjects due to an SAE of second-degree AV block and 1 subject due to an SAE of ECG QT prolongation, somnolence, and vertigo. The fifth SAE reported in 1 subject on Day 1, pyrexia, did not lead to discontinuation.

Discontinuation due to TEAEs

Ten (2.3%) subjects reported a TEAE on Day 1 (ie, following the first dose of ponesimod on Day 1 [10 mg]) leading to study discontinuation.

Nine of these subjects were discontinued due to TEAEs in the Cardiac disorders SOC and 1 subject was discontinued due to TEAEs of ECG QT prolongation, somnolence, and vertigo.

In Study B301, initiation of ponesimod using the gradual up-titration regimen (starting with ponesimod 2 mg), was not associated with clinically significant bradyarrhythmia events; none of the reported bradyarrhythmia events was serious or leading to discontinuation of treatment, no second degree or higher AV blocks were reported.

Blood pressure

In the long-term pool, mean increases of <5 mmHg from baseline in SBP/DBP were observed during treatment with ponesimod 20 mg.

In the ponesimod 20 mg group, the estimated mean absolute change from baseline in DBP to the last available on-treatment DBP value (up to EOT+1 day) based on MMRM analysis in subjects with at least 1 follow-up visit was 2.68 mmHg (n=188), and it returned to 1.57 mmHg (n=148) at FU Day 30. The estimated mean absolute change from baseline in SBP to the last available on treatment value (up to EOT+1 day) was 3.45 mmHg (n=188), and it returned to 0.81 mmHg (n=148) at FU Day 30, which was close to baseline level, indicating reversibility of BP increase upon ponesimod treatment discontinuation.

In the long-term pool, treatment-emergent increases of ≥20 mmHg from baseline in SBP were reported for 25.3% of subjects in the ponesimod 20 mg group. Treatment-emergent increases of ≥15 mmHg from baseline in DBP were reported for 25.7% of subjects in the ponesimod 20 mg group.

QT-events

The effect on the QT interval was examined in animal studies (anaesthetised dogs) and the phase 1 study 110.

Treatment with multiple-dose ponesimod at 40 mg and 100 mg (2 and 5 fold higher than the proposed maintenance dose) at steady state in healthy subjects resulted in mild prolongation of QTcI with a mean peak effect on ΔΔQTcI of 6.9 ms (upper bound of 90% 2-sided CI: 11.3 ms) with 40 mg ponesimod, and 9.1 ms (upper bound of 90% CIs: 14.0 ms) with 100 mg ponesimod. Graphical exploration of the data indicated a lack of delayed effects. There was no consistent signal of increased incidence of QTcI outliers associated with ponesimod treatment, either as absolute values (QTcI >480 ms) or change (QTcI increase >60 ms) from baseline. All incidences of QT prolongation reported during the study were considered to be not clinically significant

In the long-term pool, no TEAEs of torsade de pointes, ventricular tachycardia, or ventricular tachyarrhythmia were reported.

Echocardiograph

Echocardiograph (ECHO) was performed during Studies B201/B202 at centres with adequate expertise. This assessment was only performed for a subset of subjects: a total of 79 subjects (26, 24, 29, subjects in the ponesimod 10 mg, 20 mg, and 40 mg groups, respectively) were included in the ECHO analysis set.

A total of 5 (19.2%), 12 (50.0%), and 11 (37.9%) subjects in the 10 mg, 20 mg, and 40 mg dose groups (ECHO analysis set) had at least 1 treatment-emergent abnormal ECHO finding duringAP1. The majority of these findings were related to cardiac valves regurgitation findings, which largely consisted of trace

mitral valve, tricuspid valve, and pulmonic valve regurgitation findings. Mild regurgitation findings were observed at low incidences in all dose groups. No moderate or severe regurgitation findings were observed.

Expert opinion following a review of ECHO data in Studies B201/B202 was that ponesimod did not result in clinically significant changes in cardiac structure or left ventricular ejection fraction. Likewise, the changes in valvular structure and the trace/mild regurgitation observed in the aortic, mitral, pulmonic, and tricuspid valves are not clinically significant.

Hepatic effects

ALT: In the long-term pool, a mean increase from baseline was observed. Mean changes from baseline ranged from -2.5 to 33.7 U/L (ponesimod 20 mg group). The mean change from baseline to last on-treatment assessment was 11.4 U/L in the ponesimod 20 mg group, and mean change from baseline to last FU assessment was 6.0 U/L, indicating reversibility of the ALT increase upon ponesimod treatment discontinuation.

AST (aspartate aminotransferase): In the long-term pool, a mean increase from baseline was observed. Mean changes from baseline ranged from -0.2 to 17.7 U/L (ponesimod 20 mg group). The mean change from baseline to last on-treatment assessment was 5.8 U/L in the ponesimod 20 mg group, and mean change from baseline to last FU assessment was 2.9 U/L, indicating reversibility of the AST increase upon ponesimod treatment discontinuation.

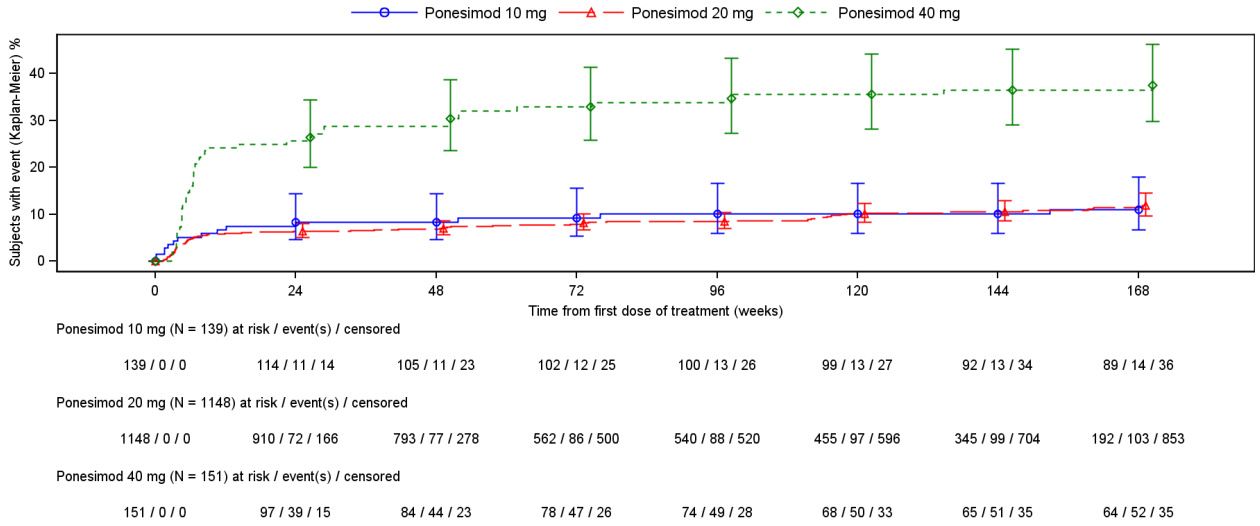
Alkaline phosphatase: In the long-term pool, a mean increase from baseline was observed. Mean changes from baseline ranged from -3.5 to 15.4 U/L (ponesimod 20 mg group).

Total bilirubin: In the long-term pool, mean changes from baseline ranged from -0.09 to 1.24 µmol/L and were unremarkable in ponesimod 20 mg group.

Effect on Pulmonary function

In the long-term pool, treatment with ponesimod 40 mg was associated with a higher risk of pulmonary AESIs as shown by the early and wide separation between the 40 mg Kaplan-Meier curve and the 10 mg and 20 mg Kaplan-Meier curves (Figure 17).

Figure 17: Kaplan-Meier Analysis of Time to First Treatment-emergent AESIs by Grouping Term: Pulmonary Events; Analysis set: Long-term Pool Analysis Set [168 weeks]



Subjects are summarised under their first randomised/allocated ponesimod dose group.
Weeks where any one arm has < 10% of subjects at risk are not displayed.
Bars show 95% CI (CI=Confidence Interval). Greenwood's formula is used for CI of Kaplan-Meier estimates; CIs are point-wise intervals.

The proportion of subjects with at least one pulmonary AESI was 22.3%, 9.8% and 42.4%, for ponesimod 10mg, 20mg and 40mg, respectively (Table 22). The event rate per 100 subject-years was 7.035, 5.682, and 15.077 in the ponesimod 10 mg, 20 mg, and 40 mg groups, respectively, indicating that the effect of ponesimod on pulmonary function was similar at ponesimod 10 mg and 20 mg dose levels, but markedly worse at the 40 mg dose level.

The PTs that were reported in more than one subject were dyspnea, obstructive airways disorder, forced expiratory volume decreased, asthma, pulmonary function tests (PFT) decreased, dyspnoea at rest, forced vital capacity (FVC) decreased, dyspnoea exertional, bronchial obstruction, and bronchospasm in the ponesimod 20 mg group (Table 22).

Table 22: Treatment-emergent Pulmonary AESIs, by Preferred Term (Frequency) Analysis Set: Long-term Pool Analysis Set

AESI category Preferred term	Ponesimod 10 mg N = 139 n (%)	Ponesimod 20 mg N = 1148 n (%)	Ponesimod 40 mg N = 151 n (%)
Subjects with at least one event	31 (22.3)	113 (9.8)	64 (42.4)
Dyspnoea	10 (7.2)	52 (4.5)	22 (14.6)
Obstructive airways disorder	7 (5.0)	19 (1.7)	8 (5.3)
Forced expiratory volume decreased	9 (6.5)	16 (1.4)	16 (10.6)
Asthma	5 (3.6)	16 (1.4)	7 (4.6)
Pulmonary function test decreased	4 (2.9)	4 (0.3)	8 (5.3)
Forced vital capacity decreased	6 (4.3)	3 (0.3)	7 (4.6)
Dyspnoea exertional	0	3 (0.3)	5 (3.3)
Bronchial obstruction	0	3 (0.3)	4 (2.6)
Dyspnoea at rest	0	4 (0.3)	1 (0.7)
Bronchospasm	0	3 (0.3)	0
Wheezing	0	1 (0.1)	2 (1.3)
Carbon monoxide diffusing capacity decreased	0	1 (0.1)	0
Allergic respiratory symptom	0	0	1 (0.7)
Pulmonary function test abnormal	0	0	1 (0.7)

AESI category Preferred term	Ponesimod 10 mg N = 139 n (%)	Ponesimod 20 mg N = 1148 n (%)	Ponesimod 40 mg N = 151 n (%)

PTs are based on MedDRA version 21.0.
Subjects are summarised under their first randomised/allocated ponesimod dose group.

The changes in FEV_1 and diffusion lung capacity for carbon monoxide (DL_{CO}) appear to be partially reversible after treatment discontinuation.

Bronchodilator assessment was introduced to test the reversibility in case of decrease in PFT. Administration of a bronchodilator (salbutamol/albuterol) led to an increase in the mean percentage predicted FEV_1, suggesting that bronchodilators are able to rapidly reduce the effects of ponesimod on PFT variables.

Seven (1.2%) subjects discontinued ponesimod because of pulmonary AEs, and 0.2% of subjects had serious pulmonary AESIs. In the updated safety report an additional 3 subjects discontinued due to obstructive airway disorder, dyspnea and decrease in FVC values of 29% less than from core baseline.

Macular Oedema

An independent Ophthalmology Safety Board (OSB) reviews in a blinded fashion any reports of macular oedema in the ponesimod clinical development programme.

A total of 20 (out of 1438) ponesimod-treated subjects in MS programme reported a suspected macular oedema AESI based on PT search criteria pre-defined in OSB charter.

Fourteen subjects reported the PT of macular oedema, 4 subjects reported papilledema, 1 subject reported cystoid macular oedema, and 1 subject reported macular hole.

The OSB confirmed diagnosis of macular oedema in 12 subjects (11 subjects with the PT of macular oedema and 1 subject with the PT of cystoid macular oedema).

Among the 12 subjects with a confirmed diagnosis of macular oedema, 10 had a medical history or concomitant eye disorder including uveitis, retinal break, vitreous detachment, diabetes mellitus, diabetic retinopathy, retrobulbar optic neuritis, cataract surgery, optic nerve atrophy, retinal angiopathy, epiretinal fibrous proliferation, altered vitreoretinal interface, and MS-associated macular oedema.

Confirmed events of macular oedema in all 12 subjects resolved (with or without sequelae). In 3 subjects, macular oedema was reported as resolved with sequelae (not specified). According to the OSB evaluation, there was a complete resolution of oedema in 2 subjects.

Neurological effects (including convulsion)

Based on observations with other S1P receptor modulators and the known MS comorbidities, seizure was included as an AESI.

In the long-term pool, a total of 16 (out of 1438) ponesimod-treated subjects reported a seizure AESI. Half of the cases were reported during the first 48 weeks of treatment.

One percent (1.0%) of subjects in the ponesimod 20 mg group had a seizure AESI. The PTs that were reported in more than 1 subject were epilepsy and partial seizures with secondary generalisation (3 subjects, 0.3%), and seizure (2 subjects, 0.2%) in the ponesimod 20 mg group. In the ponesimod 20 mg group, 3 subjects (0.3%) had serious seizure AESIs and 1 subject had a seizure AESI that led to treatment discontinuation.

The event rate per 100 subject years is 0.696 in the ponesimod 20 mg group.

In the long-term pool, no TEAEs of posterior reversible encephalopathy syndrome (PRES) or reversible cerebral vasoconstriction syndrome were reported.

Laboratory findings

In the long-term pool, changes from baseline in mean levels of clinical chemistry tests (other than liver tests) were observed in the ponesimod 20 mg group, which are not considered clinically important.

In Study B301, mean changes from baseline up to Week 108 for creatinine, creatinine clearance, albumin, glucose, potassium, and sodium were small and similar for the ponesimod 20 mg and teriflunomide 14 mg groups.

Mean changes from baseline by visit up to Week 108 in triglycerides ranged from 0.145 to 0.262 mmol/L in the ponesimod 20 mg group compared to -0.127 to 0.015 mmol/L in the teriflunomide 14 mg group. For cholesterol, mean changes from baseline by visit up to Week 108 ranged from 0.093 to 0.382 mmol/L in the ponesimod 20 mg group compared to -0.186 to -0.004 mmol/L in the teriflunomide 14 mg group. Treatment-emergent increases from baseline to >7.75 mmol/L in cholesterol were reported for 8.0% of subjects in the ponesimod 20 mg group compared to 3.5% in the teriflunomide 14 mg group.

A total of 10.1% and 8.8% of subjects in the ponesimod 20 mg and teriflunomide 14 mg groups, respectively, had elevated potassium levels >5.5 mmol/L.

Similar effects on triglycerides and cholesterol were observed in Study B201.

The applicant performed several haematological tests examining the changes in blood differential parameters. In the long-term pool, the proportions of subjects with markedly abnormal low haematology leukocytes, eosinophils, neutrophils, platelets, haemoglobin, haematocrit) values was <2.0% except for lymphocytes. These were not clinically meaningful changes.

Safety in special populations

No specific safety related differences were observed based on sex, race or geographical region.

Limitation for the safety assessment in special populations is a very small number of enrolled patients older than 55 years and no patients older than 58 years.

Ponesimod has not been studied in pregnant and/or breastfeeding women. Nonclinical studies in pregnant rats and rabbits demonstrated ponesimod-induced developmental toxicity, including increased number of foetal malformations and embryolethality. Reproductive toxicity has been acknowledged also for other S1P receptor modulators.

The current MAA does not include paediatric patients. However, PIP for children from 10 years of age has been approved in April 2018.

Immunological events

Not applicable

Safety related to drug-drug interactions and other interactions

Ponesimod metabolism is mediated by multiple, independent P450, non-P450 Phase I, and Phase II metabolic reactions

In vitro studies suggest that ponesimod and the metabolite M13 are unlikely to cause DDI at concentrations associated with therapeutic dosing of 20 mg ponesimod via inhibition or induction of cytochrome P450 enzymes, or inhibition of transporters.

Ponesimod did not affect the PK of ethinyl estradiol and norethisterone (Ortho-Novum®). Therefore, concomitant use of ponesimod is not expected to decrease the efficacy of hormonal contraceptives. No interaction studies have been performed with oral contraceptives containing other progestogens; however, an effect of ponesimod on their exposure is not expected.

Concomitant administration of atenolol (50 mg) or diltiazem (240 mg) with a single dose of 10 mg ponesimod (without up-titration) in Study 111 suggested an additive PD effect on HR and AV conduction. Bradycardia and AV blocks were observed in both atenolol and diltiazem arms of this study, including one life-threatening collapse with a 1-minute and 20-second asystole occurred after administration of concomitant treatment of 50 mg atenolol and 10 mg of ponesimod as a single dose without titration. This study was terminated for safety reasons. No significant changes in the PK of ponesimod, atenolol or diltiazem were observed in the limited number of subjects (n=5) who completed the study.

In a second DDI study, using the gradual up-titration regimen (as applied in Phase 3) (Study 117), ponesimod was administered to subjects receiving beta-blocker propranolol (80 mg) once daily at steady state. No clinically relevant changes in the PK of ponesimod, propranolol, or 4-hydroxypropranolol were observed. Concomitant administration resulted in an additive effect on HR. The mean maximum decrease in mean hourly HR from time-matched baseline for the combination of ponesimod with propranolol compared to ponesimod alone was 12.4 bpm and was observed on Day 5 (first dose of ponesimod 2 mg) and was 7.4 bpm on Day 19 (the first 20 mg dose after up-titration). The lowest mean of the HR nadir was 48.9 bpm observed on Day 7 (third day of the ponesimod up-titration regimen, when 3 mg ponesimod was administered) and increased to 54.1 bpm on Day 19. There were no drug-related SAEs in the study. No second degree or higher AV block, or clinically significant sinus pause (>3 seconds) was observed. Based on limited experience with concomitant use of beta-blockers in MS studies, ponesimod did not appear to increase the risk for cardiovascular events.

Discontinuation due to adverse events

Due to the old up-titration regimen used and the first-dose effects of ponesimod, AEs leading to ponesimod treatment discontinuation on Day 1 were reported at a higher rate in B201 study than in Study B301. Nine of 341 ponesimod-treated subjects (2.6%) in Study B201 reported TEAEs in the Cardiac disorders SOC that led to discontinuation of study treatment after receiving the first dose of ponesimod 10 mg. These TEAEs were mostly in the Cardiac disorders SOC (second degree AV block, bradycardia, palpitations, first degree AV block, AV dissociation, rhythm idioventricular) and 1 subject was discontinued due to TEAEs of ECG QT prolongation, somnolence, and vertigo. In contrast, in B301 study, none of the reported AEs was serious or led to discontinuation of ponesimod.

In the long-term pool, the incidence of TEAEs leading to discontinuation of study treatment was 8.4% in the ponesimod 20 mg group. In the ponesimod 20 mg group, the SOCs with the most commonly (≥1%) reported TEAEs leading to discontinuation of study treatment included investigations (1.6%), eye disorders (1.0%), respiratory, thoracic and mediastinal disorders (1.0%); and the most commonly (≥0.5%) reported TEAEs leading to discontinuation of study treatment were macular oedema (1.0%), dyspnoea (0.8%), and ALT increased (0.5%).

Post marketing experience

Not applicable

2.6.1. Discussion on clinical safety

The safety database consists of the data from the phase 2 and phase 3 studies, which comprises a total of 2205 subjects exposed to ponesimod, including 1438 MS subjects. In the long-term pool, the cumulative exposure with interruptions excluded was 4,094.28 subject-years in the total ponesimod group. A total of 1,027 (71.4%), 785 (54.6%), 253 (17.6%), and 41 (2.9%) subjects had exposure of at least 1, 2, 5, and 9 years, respectively. The safety database on ponesimod can be considered sufficient to allow for conclusions on safety.

The applicant presented pooled analysis for 6 months (n=108 (10 mg), n=679 (20 mg) and n=119 (40 mg)), 2 years (n=139 (10 mg), n=710 (20 mg) and n=151 (40 mg)) and long-term safety data (n=139 (10 mg), n=1148 (20 mg) and n=151 (40 mg)). However, due to differences in titration regimen these should be interpreted with caution.

Three doses i.e. 10 mg, 20 mg and 40 mg ponesimod were evaluated and compared to 14 mg teriflunomide.

The frequency of reported AEs is comparable between 20 mg ponesimod and 14 mg teriflunomide, i.e. 88.8% and 88.2% for ponesimod 20 mg and teriflunomide 14 mg, respectively. Comparable frequency between ponesimod 20 mg and teriflunomide are also reported for the majority of SOC.

The AESI were infections, malignancies, cardiovascular effects, pulmonary effect, increased liver enzymes, macular oedema and neurological events. These were in line with the known safety profile for S1P modulators. The abnormalities induced by ponesimod were reversible after 2 years of treatment for the effect on cardiac, pulmonary and hepatic parameters. It is unclear if the reversibility remains following longer exposure.

The majority of the AEs reported appears mild to moderate in nature. However, as the applicant does not always make a clear distinction between serious and severe AEs, it is not always clear for the safety of special interest whether the AEs were severe. Considering the withdrawal due to AEs, this appears not to be the case.

In Study B301, a higher proportion of subjects experienced an AE leading to treatment discontinuation in the ponesimod treatment arm compared to the teriflunomide treatment arm, i.e. 8.7% vs 6.0% respectively. The most commonly reported AEs leading to premature discontinuation by PT were dyspnoea (1.1% ponesimod 20 mg versus 0 teriflunomide 14 mg), increased ALT (0.9% vs 1.1%), and macular oedema (0.9% vs 0). These are known safety concerns related to treatment with S1P modulators. The SmPC currently has sufficient warning concerning infections and macular oedema, the AEs in the SOC eye disorders leading to withdrawal. Additionally, macular oedema, a well-known class effect of S1P modulators, has been included as an important identified risk in the RMP. Furthermore, strict recommendations for patient discontinuation from the treatment due to potential hepatotoxicity have been added to the SmPC. In order to avoid severe drug-induced hepatotoxicity, it is recommended to withdraw patients from the treatment if ALT exceeds >3 times ULN (upper lower normal) and total bilirubin > 2 times ULN.

A dose proportionate effect is observed for the AEs dyspnoea (4.6%, 6.1% and 14.3%), cough (0.9%, 2.6% and 6.7%) and peripheral oedema (0.9%, 2.6% and 10.9%). This is expected as these AEs are related to the class effect of ponesimod.

Due to the known safety profile of S1P modulators patients with active infections, hepatic impairment, severe cardiac conditions and severe pulmonary compromised patients were excluded. Therefore, these patients are either contraindicated or additional warnings and precautions are included in the SmPC to ensure safe use due to the known risks associated with the use in these populations. Moreover, bronchoconstriction and severe liver injury are included in the RMP as important identified risk and important potential risk, respectively.

S1P modulators are known to have first dose effects, i.e. bradyarrhythmia and AV conduction. The applicant used 2 titration regimens during the clinical programme, i.e. a 15-days up-titration from 2 mg to the maintenance dose of 20 mg (2-2-3-3-4-4-5-6-7-8-9-10-10-10-20 mg) and an up-titration starting from 10 mg given for 7 days, followed by the 20 mg dose. Following the up-titration with a start dose of 10 mg, bradyarrhythmia and secondary AV block were observed at first dose leading to withdrawal in 10 (2.3%) subjects. No subjects withdrew due to AEs on the first day following the 2 mg up titration regimen.

In Study AC-058-115, at day 2 of dosing the maximum mean decrease of HR was 6 bpm and 12 bpm for the 2 mg and 10 mg first titration dose, respectively. From day 3, the difference in HR was negligible, indicating that tolerance may have been developed.

Also, the incidence of bradycardia for the titration starting at 2 mg was 0.53%, while this was 0.89% for the titration starting at 10 mg. As the 2 mg titration regimen has a favourable safety profile, this regimen is proposed.

Upon request, the applicant clarified that the evaluation of risk factors for symptomatic bradyarrhythmia will be done in all patients before initiation of ponesimod treatment. Evaluation will include an ECG to determine possible pre-existing risk factors. Recommendations are included in section 4.4 of the SmPC based on the results of the clinical studies. These recommendations are consistent with the label recommendations of other S1P modulators. Additionally, "bradyarrhythmia occurring post-first dose" has been added as an important identified risk in the RMP.

No dose-related effect was seen for infection and infestations. In the long-term pool a similar frequency of infections and infestation is reported for ponesimod 10 mg and 40 mg of 70.5% and 70.9%, respectively. A substantial lower frequency of 48.3% is reported for ponesimod 20 mg. The same trend is observed for the 6-month pooled analysis, i.e. 40.7%, 27.0% and 36.1%, for ponesimod 10 mg, 20 mg and 40 mg, respectively. The trend is barely observed in the 2-year pooled analysis where the frequency of infections and infestations reported per treatment was 50.7% for 10 mg, 54.6% for 20 mg and 60.3% for 40 mg ponesimod. The reason for this could be related to differences in pool size, different titration regimens, etc. and further clarification is not considered required. In line with other S1P modulators, serious opportunistic infections including PML have been considered as important potential risks and therefore, dedicated warnings have been included in section 4.4 of the SmPC. Similarly, skin cancer and non-skin malignancy are identified as important potential risks in the RMP and will be active monitored in the PSURs.

The incidence of adverse events in the reproductive and breast disorders SOC was comparable between ponesimod and teriflunomide, 28 (5.0%) for ponesimod 20mg and 34 (6.0%) in the teriflunomide 14mg group. However, the applicant agrees that these AEs are anticipated bases on non-clinical data, mechanistic data and findings in products of the same class. Therefore, the applicant propose during the procedure the inclusion of the relevant statement in the SmPC including the contraindication in during pregnancy and in women of childbearing potential not using effective contraception (SmPC 4.3). Additionally, it is supported that reproductive and embryofetal toxicity is addressed as an important potential risk in the safety concerns of the RMP and actively monitored in the PSUR.

During the procedure, the applicant was invited to further discuss on reported TEAEs in the SOC of Psychiatric disorders. It was clarified that subjects with reported TEAEs in the SOC of psychiatric disorders had a psychiatric disorder at baseline. The provided clarification is considered acceptable and further analysis suggests that there are no specific psychiatric safety issues related to ponesimod use.

One percent (1.0%) of subjects in the ponesimod 20 mg group had a seizure AESI and in the long-term pool, a total of 16 (out of 1438) ponesimod-treated subjects reported a seizure AESI. In line with other S1P receptors, convulsions are included as a potential important risk in the RMP to be actively monitored in the PSUR.

Several post-marketing case reports revealed an increased risk of paradoxically expanded inflammatory, demyelinating lesions (i.e. PRES) in patients treated with other S1P modulators. Although, the role of S1P receptor modulators in the development of such lesions is not completely clear, increased risk associated with exposure to S1P receptor modulators cannot be excluded. Therefore, the applicant has supplemented the safety information in the SmPC Section 4.4. of the SmPC by cautionary statements and has included "Unexpected neurological or psychiatric signs and symptoms (e.g. PRES, ADEM, atypical MS relapses)" as an important potential risk in the RMP to follow this up further in a post-marketing setting.

A total of 5 subjects died during the full clinical programme of ponesimod, e.g. not restricting to the MS indication. Three subjects were treated with ponesimod and 2 subjects with teriflunomide. Although the applicant indicates that this was not related to the treatment with ponesimod, this cannot be excluded, as the subjects had either pre-existing cardiac conditions or pre-existing hepatic impairment. Considering the effect of ponesimod on both the hepatic and cardiac system, this cannot be fully excluded.

The applicant investigated concomitant treatment with hormonal contraceptive, beta-blockers and calcium channel blockers. No effect on either the PK of PD was observed for hormonal contraceptive. An additive effect on the HR was observed for concomitant administration with beta-blockers and calcium channel blockers. In the first study which examined the concomitant use of beta-blockers and calcium channel blockers in healthy volunteers, 18 of the 23 subjects withdrew due to SAEs. This appeared to be related to the first dose effect of ponesimod. Study 117 showed that although an additive effect on HR is observed when beta-blockers are administered when ponesimod has reached a steady-state, no additional cardiac safety concerns emerged when the baseline HR was >55bpm. Therefore, ponesimod can be safely administered in subjects using a stable dose of beta-blockers and a resting HR >55. First-dose 4-hour monitoring is recommended for patients with sinus bradycardia [HR less than 55 beats per minute (bpm)], first- or second-degree [Mobitz type I] AV block, or a history of myocardial infarction or heart failure occurring more than 6 months prior to treatment initiation and in stable condition. This is also included in section 4.4 of the SmPC.

Due to the limited long-term safety data and lack of data in elderly subjects, the applicant proposes to include these as missing information in the RMP. This is agreed to acquire more data. An additional post-marketing study is not deemed necessary as these can be followed in a regular PSUR. However, it was questioned whether the submitted safety data could be generalised to older patients with late onset MS, especially considering potential hepatotoxicity and cardiovascular effects. The popPK modelling did not identify any specific age-related safety issues. However, clinical studies of ponesimod did not include patients aged 65 years and older as stated in section 4.2. of the SmPC Furthermore, a specific warning has been added to Section 5.2 of the SmPC, therefore the proposed measures in the RMP are considered adequate.

2.6.2. Conclusions on the clinical safety

The applicant provided an elaborate and complete analysis of the safety of ponesimod in MS patients.

In general, ponesimod displays a risk profile that resembles in many respects the risk profile of other S1P receptor modulators, i.e. an increased risk for infection, bradyarrhythmia and AV conduction, increased liver enzymes, bronchoconstriction, macular oedema and teratogenicity.

The SmPC of ponesimod covers this as the use in severe cardiac impaired, i.e. NYHA class III or IV heart failure and second or third degree AV block, and use in pregnancy is contraindicated. In addition warnings and precautions are included for bradyarrhythmia associated with the first dose effect (regardless of having known heart conditions), (skin) malignancies, increased risk for infections, macular oedema, bradyarrhythmia and atrioventricular conduction delay, respiratory effect, liver injury and encephalopathy syndrome. These will also be monitored in a post-marketing setting.

The role of S1P receptor modulators in the development of paradoxically expanded inflammatory, demyelinating lesions (i.e. PRES) is included in the RMP for post-marketing monitoring. However, the effect on respiratory impairment should also be monitored post-marketing as the effect on respiratory decline is only partially reversible when discontinuing the treatment.

Overall, the safety profile of ponesimod does not lead to a negative B/R, as the safety profile is well known, can be monitored, and has been accepted for other S1P modulators.

2.7. Risk Management Plan

Safety concerns

Table 23: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Bradyarrhythmia occurring post-first dose Macular oedema Bronchoconstriction
Important potential risks	Severe liver injury Serious opportunistic infections including PML Skin cancer Non-skin malignancy Reproductive and embryofoetal toxicity Convulsions Unexpected neurological or psychiatric symptoms/signs (e.g.: PRES, ADEM, Atypical MS Relapses)
Missing information	Use in elderly patients Long-term safety of ponesimod

ADEM: acute disseminated encephalomyelitis; MS: multiple sclerosis; PRES: posterior reversible encephalopathy syndrome.

Pharmacovigilance plan

Table 24: On-going and planned additional pharmacovigilance activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	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				
Ponesimod Pregnancy Outcomes Enhanced Monitoring (POEM) Planned	To prospectively collect and evaluate safety data on pregnancy outcomes and on the risk of birth defects in the offspring of women exposed to ponesimod immediately before (up to 1 week before last menstrual period) and during pregnancy	Reproductive and embryofetal toxicity	Interim report	Not applicable. Periodic updates will be provided in the PBRER
			Final report	1 year after the end of data collection
AC-058B303/ OPTIMUM-LT Multicentre, non-comparative extension to study AC-058B301, to investigate the long-term safety, tolerability, and control of disease of ponesimod 20 mg in subjects with relapsing multiple sclerosis Ongoing	To describe the long-term safety and tolerability of ponesimod 20 mg in subjects with RMS as well as the effects of re-initiation of ponesimod treatment after interruption in subjects with RMS	• Bradyarrhythmia occurring post-first dose • Bronchoconstriction • Severe liver injury • Serious opportunistic infections including PML • Skin cancer • Non-skin malignancy • Convulsions • Unexpected neurological or psychiatric symptoms/signs (PRES, ADEM, atypical MS relapses) • Long-term safety of ponesimod	Final report	15/02/2025

AC-058B202 Multicentre, randomised, double-blind, parallel-group extension to study AC-058B201 to investigate the long-term safety, tolerability, and efficacy of 10, 20, and 40 mg/day ponesimod, an oral $S1P_1$ receptor agonist, in patients with relapsing-remitting multiple sclerosis Ongoing	To investigate the long-term safety and tolerability of ponesimod	• Bronchoconstriction • Severe liver injury • Serious opportunistic infections including PML • Skin cancer • Non-skin malignancy • Convulsions • Unexpected neurological or psychiatric symptoms/signs (PRES, ADEM, atypical MS relapses) • Long-term safety of ponesimod	Final report	14/12/2024
Survey among healthcare professionals (neurologists treating patients with MS along with MS specialist nurses) in selected European countries to evaluate knowledge and behaviors required for the safe use of ponesimod Planned	To determine the effectiveness of HCP and patient/caregiver educational materials. The survey will evaluate whether the target audience received the educational materials, and will assess the HCP's knowledge and HCP's perception of the patient's/caregiver's knowledge of key messages for the safe use of ponesimod, and behaviors associated with safety concerns covered by the educational materials.	• Bradyarrhythmia occurring post-first dose • Macular oedema • Bronchoconstriction • Severe liver injury • Serious opportunistic infections including PML • Skin cancer • Reproductive and embryofetal toxicity • Convulsions • Unexpected neurological or psychiatric symptoms/signs (PRES, ADEM, atypical MS relapses)	Interim report	Not applicable. Periodic updates will be provided in the PBRER
			Final report	1 year after the end of data collection

ADEM: acute disseminated encephalomyelitis; HCP: healthcare professional; PBRER: Periodic Benefit-Risk Evaluation Report; PML: progressive multifocal leukoencephalopathy; PRES: posterior reversible encephalopathy syndrome; RMS: relapsing multiple sclerosis; MS: multiple sclerosis.

Risk minimisation measures

Table 25: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
Bradyarrhythmia occurring post-first dose	**Routine risk minimisation measures:** • SmPC Section 4.2 • SmPC Section 4.3 • SmPC Section 4.4 • SmPC Section 4.5 • SmPC Section 4.8 • SmPC Section 4.9 • SmPC Section 5.1 • PL Section 2 • PL Section 3 • PL Section 4 • An ECG should be obtained before treatment initiation with ponesimod and before treatment re-initiation when 4 or more consecutive doses are missed, as described in SmPC Sections 4.2 and 4.4, and PL Section 2. • Ponesimod treatment must be started with a 14-day up-titration scheme using a treatment initiation pack which should also be used before treatment re-initiation if 4 or more consecutive doses are missed, as described in SmPC Sections 4.2 and 4.4 and PL Section 3. • Advice from a cardiologist should be sought before treatment initiation with ponesimod if treatment is considered in patients with certain pre-existing heart conditions, as described in SmPC Section 4.4. Before starting treatment, patients are advised to tell their doctor if they have certain heart or blood vessel conditions, have suddenly passed out or fainted, as described in PL Section 2. • First-dose monitoring is recommended for patients with certain heart conditions, as described in SmPC Section 4.4 and PL Section 2.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • Trial AC-058B303/ OPTIMUM-LT Final report: 15/02/2025 • HCP survey to assess the effectiveness of HCP and patient/caregiver educational materials Final report: 1 year after the end of data collection

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	• Appropriate management should be initiated in case certain post-dose heart-related disorders or symptoms occur, as described in SmPC Section 4.4. • Advice from a cardiologist should be sought before treatment initiation with ponesimod if treatment is considered in patients who receive concomitant therapy with medicinal products that decrease HR. Switching to non-HR-lowering medicinal products should be considered, as described in SmPC Section 4.4. Patients are advised to tell their doctor or pharmacist, before starting treatment, if they are taking, have recently taken or might take any medicine to control the heart rhythm or heart beat, as described in PL Section 2. • Patients who receive an overdose of ponesimod, especially upon initiation/re-initiation of treatment, should be observed for signs and symptoms of bradycardia as well as AV conduction blocks, which may include overnight monitoring, as described in SmPC Section 4.9. • Patients who experience signs and symptoms indicative of slow HR should call their physician immediately, as described in PL Section 2. • Pack size: ponesimod treatment initiation pack for 14-day up-titration • Legal status: medicinal product subject to restricted medical prescription **Additional risk minimisation measures:** • Healthcare professional checklist • Patient/caregiver guide	
Macular oedema	**Routine risk minimisation measures:** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • An ophthalmic evaluation of the fundus, including the macula, is recommended in all patients before ponesimod treatment initiation and again at any time if a patient reports any change in vision while on ponesimod therapy, as described in SmPC Section 4.4 and PL Section 2. • Ponesimod therapy should not be initiated in patients with macular oedema until resolution, and patients with visual symptoms of macular oedema should be evaluated and, if confirmed, treatment should be discontinued, as described in SmPC Section 4.4. • Patients with a history of uveitis or diabetes mellitus should have regular examinations of the fundus, including the macula, prior to treatment initiation with ponesimod, and	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • HCP survey to assess the effectiveness of HCP and patient/caregiver educational materials Final report: 1 year after the end of data collection

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	have follow-up evaluations while receiving therapy, as described in SmPC Section 4.4. Before starting treatment, patients are advised to tell their doctor, if they have diabetes or eye problems, as described in PL Section 2. • Patients who experience symptoms of macular oedema should call their physician immediately, as described in PL Sections 2 and 4. • Legal status: medicinal product subject to restricted medical prescription **Additional risk minimisation measures:** • Healthcare professional checklist • Patient/caregiver guide	
Bronchoconstriction	**Routine risk minimisation measures:** • SmPC Section 4.4 • SmPC Section 4.8 • SmPC Section 5.1 • PL Section 2 • PL Section 4 • Spirometry evaluation of respiratory function should be performed during ponesimod therapy, if clinically indicated, as described in SmPC Section 4.4. • Patients who develop new or worsening breathing problems should call their physician immediately, as described in PL Sections 2 and 4. Before starting treatment, patients are advised to tell their doctor if they have breathing problems, as described in PL Section 2. • Legal status: medicinal product subject to restricted medical prescription **Additional risk minimisation measures:** • Healthcare professional checklist • Patient/caregiver guide	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • Trial AC-058B303/ OPTIMUM-LT Final report: 15/02/2025 • Trial AC-058B202 Final report: 14/12/2024 • HCP survey to assess the effectiveness of HCP and patient/caregiver educational materials Final report: 1 year after the end of data collection
Important Potential Risks		
Severe liver injury	**Routine risk minimisation measures:** • SmPC Section 4.2 • SmPC Section 4.3 • SmPC Section 4.4 • SmPC Section 4.8 • SmPC Section 5.2 • PL Section 2 • PL Section 4 • Recent (ie, within the last 6 months) transaminase and bilirubin levels should be reviewed before treatment initiation with ponesimod, as described in SmPC Section 4.4 and PL Section 2. • Patients who develop symptoms suggestive of hepatic dysfunction should be monitored for hepatotoxicity. Ponesimod treatment should be discontinued in case significant	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • Trial AC-058B303/ OPTIMUM-LT Final report: 15/02/2025 • Trial AC-058B202 Final report: 14/12/2024 • HCP survey to assess the effectiveness of HCP and patient/caregiver educational materials Final report: 1 year after the end of data collection

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	liver injury is confirmed, as described in SmPC Section 4.4. • Patients who develop symptoms of liver problems should call their physician immediately, as described in PL Section 2. Before starting treatment, patients are advised to tell their doctor if they have liver problems, as described in PL Section 2. • Legal status: medicinal product subject to restricted medical prescription **Additional risk minimisation measures:** • Healthcare professional checklist • Patient/caregiver guide	
Serious opportunistic infections including PML	**Routine risk minimisation measures:** • SmPC Section 4.3 • SmPC Section 4.4 • SmPC Section 4.5 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Results from a recent (ie, within 6 months or after discontinuation of prior therapy) CBC with differential (including lymphocyte count) should be reviewed before treatment initiation with ponesimod, as described in SmPC Section 4.4 and PL Section 2.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • TFUQ to obtain structured information on reported AEs • Independent review of cases of suspected PML by external adjudication committee **Additional pharmacovigilance activities:** • Trial AC-058B303/ OPTIMUM-LT Final report: 15/02/2025 • Trial AC-058B202 Final report: 14/12/2024 • HCP survey to assess the effectiveness of HCP and patient/caregiver educational materials Final report: 1 year after the end of data collection

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	• Assessments of CBC are recommended periodically during treatment with ponesimod; confirmed absolute lymphocyte counts <0.2x10^9/L should lead to interruption of ponesimod therapy; re-initiation of ponesimod can be considered when the level reaches >0.8x10^9/L, as described in SmPC Section 4.4. • Treatment initiation with ponesimod should be delayed in patients with severe active infection until resolution. Vigilance for signs and symptoms of infection should be continued for 1 to 2 weeks after treatment discontinuation, as described in SmPC Section 4.4. Before starting treatment, patients are advised to tell their doctor if they have a fever or infection, as described in PL Section 2. • Effective diagnostic and therapeutic strategies should be used in patients with symptoms of infection while on ponesimod therapy. Suspension of ponesimod treatment should be considered if a patient develops a serious infection, as described in SmPC Section 4.4. • Patients without an HCP-confirmed history of varicella (chickenpox) or without documentation of a full course of vaccination against VZV should be tested for antibodies to VZV before treatment initiation with ponesimod, as described in SmPC Section 4.4 and PL Section 2. Before starting treatment, patients are advised to tell their doctor if they never had chickenpox (varicella) or have not received a vaccine for chickenpox, as described in PL Section 2. • Physicians should be vigilant for clinical signs or symptoms of CM. Patients with signs or symptoms consistent with a cryptococcal infection should undergo prompt diagnostic evaluation and treatment. Ponesimod treatment should be suspended until a cryptococcal infection has been excluded; if CM is diagnosed, appropriate treatment should be initiated, as described in SmPC Section 4.4. • Physicians should be vigilant for clinical symptoms or MRI findings suggestive of PML. If PML is suspected, ponesimod treatment should be suspended until PML is excluded. Treatment with ponesimod should be discontinued if PML is confirmed, as described in SmPC Section 4.4. • The half-life and mode of action of medicinal products with prolonged immune effects should be considered when switching from these medicinal products to	

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	avoid unintended additive effects on the immune system while at the same time minimizing risk of disease reactivation when initiating ponesimod, as described in SmPC Section 4.4. For the same reason, caution should be applied during concomitant administration and in the weeks following administration or, if there is a history of prior use before initiating, during and up to 1 week after the last dose of ponesimod, as described in SmPC Sections 4.4 and 4.5. • A full course of vaccination with varicella vaccine is recommended for antibody-negative patients before treatment initiation with ponesimod, and treatment should be delayed for 4 weeks after vaccination, as described in SmPC Section 4.4 and PL Section 2. • The use of live, attenuated vaccines should be avoided while on ponesimod therapy and up to 1 week after treatment discontinuation. If immunisation with a live attenuated vaccine is required, ponesimod treatment should be paused from 1 week prior to 4 weeks after a planned vaccination, as described in SmPC Sections 4.4 and 4.5 and PL Section 2. Before starting treatment, patients are advised to tell their doctor if they have recently received any vaccinations or are planning to receive a vaccination, as described in PL Section 2. • Patients who experience symptoms of infection during treatment or 1 week after the last dose should call their physician immediately, as described in PL Sections 2 and 4. • Before starting treatment, patients are advised to tell their doctor if they have an immune system that does not work properly due to a disease or are taking medicines that weaken their immune system, as described in PL Section 2. • Legal status: medicinal product subject to restricted medical prescription **Additional risk minimisation measures:** • Healthcare professional checklist • Patient/caregiver guide	

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Skin cancer	**Routine risk minimisation measures:** • SmPC Section 4.3 • SmPC Section 4.4 • SmPC Section 4.5 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Patients treated with ponesimod should be cautioned against exposure to sunlight and UV light without protection, and they should not receive concomitant phototherapy with UVB radiation or PUVA photochemotherapy, as described in SmPC Section 4.4 and PL Section 2. PL Section 2 also advises patients on how to limit such exposure. • The half-life and mode of action of medicinal products with prolonged immune effects should be considered when switching from these medicinal products to avoid unintended additive effects on the immune system while at the same time minimizing risk of disease reactivation when initiating ponesimod, as described in SmPC Section 4.4. For the same reason, caution should be applied during concomitant administration and in the weeks following administration or, if there is a history of prior use before initiating, during and up to 1 week after the last dose of ponesimod, as described in SmPC Sections 4.4 and 4.5. • Before starting treatment, patients are advised to tell their doctor if they have an immune system that does not work properly due to a disease or are taking medicines that weaken their immune system, as described in PL Section 2. • Legal status: medicinal product subject to restricted medical prescription **Additional risk minimisation measures:** • Healthcare professional checklist • Patient/caregiver guide	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • Trial AC-058B303/ OPTIMUM-LT Final report: 15/02/2025 • Trial AC-058B202 Final report: 14/12/2024 • HCP survey to assess the effectiveness of HCP and patient/caregiver educational materials Final report: 1 year after the end of data collection
Non-skin malignancy	**Routine risk minimisation measures:** • SmPC Section 4.3 • SmPC Section 4.4 • SmPC Section 4.5 • PL Section 2 • The half-life and mode of action of medicinal products with prolonged immune effects should be considered when switching from these medicinal products to avoid unintended additive effects on the immune system while at the same time minimizing risk of disease reactivation when initiating ponesimod, as described in SmPC Section 4.4. For the same reason,	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • Trial AC-058B303/ OPTIMUM-LT Final report: 15/02/2025 • Trial AC-058B202 Final report: 14/12/2024

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	caution should be applied during concomitant administration and in the weeks following administration, or if there is a history of prior use before initiating, during and up to 1 week after the last dose of ponesimod, as described in SmPC Sections 4.4 and 4.5. • Before starting treatment, patients are advised to tell their doctor if they have an immune system that does not work properly due to a disease or are taking medicines that weaken their immune system, as described in PL Section 2. • Legal status: medicinal product subject to restricted medical prescription **Additional risk minimisation measures:** • None	
Reproductive and embryofetal toxicity	**Routine risk minimisation measures:** • SmPC Section 4.3 • SmPC Section 4.4 • SmPC Section 4.6 • SmPC Section 5.3 • PL Section 2 • Before initiation of ponesimod treatment in women of childbearing potential, a negative pregnancy test result must be available, as described in SmPC Sections 4.4 and 4.6 and PL Section 2. • Women of childbearing potential should be counseled before treatment initiation on the potential for a serious risk to the fetus and the need for effective contraception during treatment with ponesimod and for 1 week after treatment discontinuation, as described in SmPC Sections 4.4 and 4.6 and PL Section 2. • Patients are advised not to use ponesimod during pregnancy, if they are trying to become pregnant, or if they could become pregnant and are not using effective contraception, as described in PL Section 2. • Ponesimod treatment should be discontinued immediately if a woman becomes pregnant during treatment, as described in SmPC Section 4.6 and PL Section 2. • If a woman becomes pregnant during treatment with ponesimod, medical advice should be given regarding the risk of harmful effects to the fetus associated with treatment. Follow-up examinations should be performed, as described in SmPC Section 4.6. Patients are advised to tell their doctor if they become pregnant within 1 week after stopping treatment, as described in PL Section 2.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • Ponesimod POEM Final report: 1 year after the end of data collection. • HCP survey to assess the effectiveness of HCP and patient/caregiver educational materials Final report: 1 year after the end of data collection

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	• Patients are advised to talk to their doctor about reliable methods of contraception, as described in PL Section 2. • Legal status: medicinal product subject to restricted medical prescription **Additional risk minimisation measures:** • Healthcare professional checklist • Patient/caregiver guide • Pregnancy-specific patient reminder card	
Convulsions	**Routine risk minimisation measures:** • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Patients who experience symptoms of a seizure should call their physician immediately, as described in PL Section 2. • Legal status: medicinal product subject to restricted medical prescription **Additional risk minimisation measures:** • Healthcare professional checklist • Patient/caregiver guide	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • TFUQ to obtain structured information on reported AEs • Cumulative reviews of events of convulsion in the PBRER **Additional pharmacovigilance activities:** • Trial AC-058B303/ OPTIMUM-LT Final report: 15/02/2025 • Trial AC-058B202 Final report: 14/12/2024 • HCP survey to assess the effectiveness of HCP and patient/caregiver educational materials Final report: 1 year after the end of data collection
Unexpected neurological or psychiatric symptoms/signs (PRES, ADEM, atypical MS relapses)	**Routine risk minimisation measures:** • SmPC Section 4.4 • PL Section 2 • A complete physical and neurological examination should be scheduled in ponesimod-treated patients who develop any unexpected neurological or psychiatric symptoms/signs, any symptom/sign suggestive of an increase of intracranial pressure, or accelerated neurological deterioration, and an MRI should be considered, as described in SmPC Section 4.4. • If PRES is suspected, ponesimod treatment should be discontinued, as described in SmPC Section 4.4. • Patients who experience symptoms suggestive of PRES should call their physician immediately, as described in PL Section 2.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • TFUQ to obtain structured information on reported AEs **Additional pharmacovigilance activities:** • Trial AC-058B303/ OPTIMUM-LT Final report: 15/02/2025 • Trial AC-058B202 Final report: 14/12/2024 • HCP survey to assess the effectiveness of HCP and patient/caregiver educational materials Final report: 1 year after the end of data collection
	• Legal status: medicinal product subject to restricted medical prescription **Additional risk minimisation measures:** • Healthcare professional checklist • Patient/caregiver guide	
Missing Information		
Use in elderly patients	**Routine risk minimisation measures:** • SmPC Section 4.2	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	• Legal status: medicinal product subject to restricted medical prescription **Additional risk minimisation measures:** • None	• Cumulative reviews of reports of ponesimod use in elderly patients in the PBRER. **Additional pharmacovigilance activities:** • None
Long-term safety of ponesimod	**Routine risk minimisation measures:** • Legal status: medicinal product subject to restricted medical prescription **Additional risk minimisation measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • Trial AC-058B303/ OPTIMUM-LT Final report: 15/02/2025 • Trial AC-058B202 Final report: 14/12/2024

ADEM: acute disseminated encephalomyelitis; AEs: Adverse Events; CBC: complete blood count; CM: cryptococcal meningitis; ECG: electrocardiogram; HCP: healthcare professional; HR: heart rate; MS: multiple sclerosis; MRI: magnetic resonance imaging; PBRER: Periodic Benefit-Risk Evaluation Report; PL: package leaflet; PML: progressive multifocal leukoencephalopathy; PRES: posterior reversible encephalopathy syndrome; PUVA: psoralen and ultraviolet A; SmPC: summary of product characteristics; TFUQ: targeted follow-up questionnaire; UVB: ultraviolet B; VZV: varicella zoster virus.

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.5 is acceptable.

2.8. Pharmacovigilance

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.

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 18.03.2021. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of ponesimod with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers ponesimod to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. 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.*

2.10.2. Labelling exemptions

Minimum particulars have been granted to be used on the blisters sealed inside a wallet (i.e. name of the medicinal product, strength, INN, EXP and Lot).

2.10.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Ponvory (ponesimod) 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

Ponesimod is an iminothiazolidinone derivative, and is an orally active, selective $S1P_1$ modulator. The proposed indication is

Ponvory is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features.

MS is an inflammatory autoimmune and neurodegenerative disorder of the CNS. This disease is characterised by a heterogeneous clinical expression, an unpredictable course, and a variable prognosis. MS is characterised by inflammation, demyelination, neuronal and oligodendrocyte loss, and disruption of the blood-brain barrier, leading to irreversible deficits in physical function and cognition and an impaired quality of life.

The aim of treating RMS with DMT is to modify the natural course of the disease by reducing the rate of relapses and the appearance of new focal inflammatory lesions in order to delay disability progression.

3.1.2. Available therapies and unmet medical need

Therapies for MS include treatments for relapse (e.g. steroids) and those that alter the course of the disease (DMTs).

There are currently several approved DMTs in MS with different efficacy and safety profiles. The injectable IFN (IFN β-1a and β-1b) and glatiramer acetate have a well-established efficacy and safety profile. Due to the rather moderate efficacy, these as well as other first-line treatments dimethyl fumarate and teriflunomide are usually prescribed to patients without high disease activity.

The monoclonal DMTs (alemtuzumab, natalizumab) are restricted to subjects with highly active disease. Because of their safety profile, the benefit-risk ratio in low active multiple sclerosis was assessed as negative. Anti-C20 monoclonal DMTs such as ocrelizumab and ofatumumab are indicated for active RRMS and RMS, respectively

There are currently three registered S1P modulators fingolimod, ozanimod and siponimod. The latter is indicated in SPMS only. The use of the first registered S1P modulator, i.e. fingolimod, has been restricted to RRMS patients with highly active disease due to its safety profile. However, recently ozanimod has been approved for a broad indication in RRMS. The safety profile of ozanimod, although similar to fingolimod, was considered manageable with the risk minimisation procedure in place, to allow a broad RRMS indication.

3.1.3. Main clinical studies

The efficacy and safety of ponesimod were examined in a single pivotal study in patients with RMS. This study was a multicentre, randomised, DB, parallel-group, active-controlled, superiority study to compare the efficacy and safety of ponesimod (N=567) to teriflunomide (N=566). The treatment period was 108 weeks, which included an up-titration period of 14 days. The study included one dose strength of ponesimod, i.e. 20 mg QD.

The study included both patients with RRMS and SPMS, with confirmed disease activity, i.e. one or more relapse with onset within the period of 12 to 1 months prior to baseline, or two or more relapses with onset within the period of 24 to 1 months prior to baseline assessment, or who had one or more Gd+ lesion(s) prior to baseline EDSS assessment.

The primary endpoint was ARR. The secondary endpoints were FSIQ-RMS, CUALs, 12-week CDA and 24-week CDA. The testing hierarchy as chosen by the applicant is not agreed, as disability progression is considered the key secondary endpoint after ARR.

3.2. Favourable effects

The ARR was 0.202 (99% CI 0.165, 0.246) in the ponesimod group as compared to 0.290 (99% CI 0.244, 0.345) in the teriflunomide group. The RR was 0.695 (99% CL 0.536, 0.902; p=0.0003).

A 12-week CDA was observed in 10.1% and 12.4% of subjects in the ponesimod 20 mg and teriflunomide 14 mg groups, respectively. The HR was 0.83 (95% CI 0.58, 1.18; p=0.2939) with ponesimod 20 mg compared to teriflunomide 14 mg.

A 24-week CDA was observed in 8.1% and 9.9% of subjects in the ponesimod 20 mg and teriflunomide 14 mg groups, respectively. The HR was 0.84 (95% CI 0.57, 1.24; nominal p=0.3720) with ponesimod 20 mg compared to teriflunomide 14 mg.

The LS mean change from baseline to week 108 in FSIQ-RMS was -0.01 (95% CI -1.60, 1.58) in the ponesimod group and 3.56 (95% CI 1.96, 5.16) in the teriflunomide groups. The difference of LS means was -3.57 (95% CL -5.83, -1.32; p=0.0019).

The mean CUALs was 1.405 (95% CI 1.215, 1.624) in the ponesimod group and 3.164 (95% CI 2.757, 3.631) in the teriflunomide group. The RR was 0.444 (95% CI 0.364, 0.542; p<0.0001).

29.3% of patients in the ponesimod experienced a relapse up to the end of the study, as compared to 39.4% of patients in the teriflunomide group. HR of time to first relapse was 0.76 (95% CI 0.62, 0.93; nominal p=0.0081)

The LS mean difference (ponesimod 20 mg − teriflunomide 14 mg) in change from baseline to Week 108 in EDSS score was −0.13 (95% CIs: −0.22, −0.04; nominal p=0.0059)

3.3. Uncertainties and limitations about favourable effects

The observed effect on fatigue, as measured by the FSIQ-RMS is not clinically relevant. As the scale was not validated in a clinical study before, it is unclear whether the lack of effect on the scale is a failure of the scale or the treatment.

Ponesimod failed to show superiority to teriflunomide in disability progression.

A limited number of patients with active SPMS was included in the study.

3.4. Unfavourable effects

In Study B301, the frequency of reported AEs was 88.8% and 88.2% for ponesimod 20 mg and teriflunomide 14 mg, respectively. The AEs occurring in at least 5% of subjects were reasonably balanced between treatment groups: nasopharyngitis (19.3% vs 16.8%), headache (11.5% vs 12.7%), upper respiratory tract infection (10.6 vs 10.4%), hypertension (8.0% vs 7.8%), nausea (7.6% vs 8.3%), fatigue (6.0% vs 6.5%), back pain (5.8% vs 6.7%), urinary tract infection (5.7% vs 5.1%), but increased for ALT increased (19.5% for ponesimod 20mg vs 9.4% teriflunomide 14mg), AST increased (6.4% vs 3.5%), dyspnoea (5.3% vs 1.2%), and decreased for depression (3.7% vs 5.1%), diarrhoea (3.5% vs 7.8%) and alopecia (3.2% vs 12.7%)

In the long term pool the AEs reported with a frequency of ≥5% in the 20 mg ponesimod group were: nasopharyngitis (17.5%), ALT increased (16.4%), headache (10.9%), upper respiratory tract infection (9.8%), hypertension (6.9%), fatigue (6.6%), back pain (6.5%), urinary tract infection (5.8%), nausea (5.2%), AST increased (5.1%).

In Study B301, serious AEs were experienced by approximately 10% of the subjects, i.e. 8.7% of the ponesimod 20mg group and 8.1% in the teriflunomide group. The serious AEs reported in >2 subjects in the 20 mg ponesimod group were appendicitis (3 subjects, 0.5%), abdominal pain (3 subjects, 0.5%). In the teriflunomide group, the serious AEs cholelithiasis occurred in more >2 subjects (3 subjects, 0.5%).

The incidence of AEs in the reproductive and breast disorders SOC was 28 (5.0%) for ponesimod 20mg and 34 (6.0%) in the teriflunomide 14mg group.

In the long-term pool, the incidence of TEAEs leading to discontinuation of study treatment was 8.4% in the ponesimod 20 mg group. In study B301, the proportion of subjects with at least 1 AE leading to treatment discontinuation was 8.7% for ponesimod 20 mg and 6.0% for 14mg teriflunomide. The most

commonly reported TEAEs leading to premature discontinuation were dyspnoea (1.1% ponesimod 20 mg versus 0 teriflunomide 14 mg), increased ALT (0.9% vs 1.1%) and macular oedema (0.9% vs 0).

A total of 3 deaths were reported in the MS phase 2/3 studies (1 subject treated with ponesimod), and two additional deaths occurred in non-MS studies. Three subjects were treated with ponesimod. The causes of death were sudden cardiac death (2 subjects) and hepatic failure (1 subject).

3.5. Uncertainties and limitations about unfavourable effects

Different up-titration regimens were used during the clinical programme; therefore, the dose-related AEs, particularly in the long-term pool should be interpreted with caution.

Comparative data to teriflunomide is not available for the long-term safety data, as subjects switched to ponesimod 20mg.

Due to the known safety profile of S1P modulators patients with active infections, hepatic impairment, severe cardiac conditions and severe pulmonary compromised patients were excluded. The SmPC has been updated to includes contraindication for these subjects and monitoring for signs of these in the section warning and precautions for use. Furthermore, these will be actively followed in the RMP.

Assessment of cardiac function including ECG is conducted in all patients starting treatment with ponesimod in order to capture patients with latent/undiagnosed arrhythmias and conduction disorders.

Additionally, bronchoconstriction is included in the RMP as an identified important risk and will be actively monitored in the PSUR.

There is limited long-term safety data and no experience of ponesimod in elderly subjects.

3.6. Effects Table

Table 26: Effects Table for Ponvory, treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features. (data cut-off: 31 March 2019)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
ARR	ARR up to EOS, defined as the number of confirmed relapses	Mean 99% CL[#]	0.202 0.165, 0.246	0.290 0.244, 0.345	**SoE**: RR 0.695 (99% CI 0.536, 0.902) P<0.0003, time to first relapse HR 0.76 (95% CI 0.62, 0.93) p=0.0081 **Un**: MAR analysis not the most realistic estimate The estimate could be biased due to potential unblinding.	Pivotal study B301
24-week CDA	Time to 24-week CDA from baseline to EOS	% of subjects	8.1%	9.9%	**SoE**: HR 0.84 (95% CI 0.57, 1.24); p=0.3720 **Un:** Also for 12-week CDA no statistically significant difference was observed.	Pivotal study B301
FSIQ-RMS	Change from baseline to Week 108 in symptoms domain of the FSIQ–RMS	Mean 95% CL	-0.01 -1.60, 1.58	3.56 1.96, 5.16	**SoE:** Diff of LS means -3.57 (95% CI -5.83, -1.32) **Un:** Not a clinically relevant change, failure of the scale or treatment?	Pivotal study B301
CUALs	CUALs from baseline to Week 108	Mean no./year 95% CL	1.405 1.215, 1.624	3.164 2.757, 3.631	**SoE:** RR 0.444 (95% CI 0.364, 0.542), P<0.0001	Pivotal study B301
Unfavourable Effects						
	Up to two years:				Long term safety profile (**up to 9 years)** , in line with short term findings	Pivotal study B301
ALT	Alanine Aminotransferase	%	19.5	9.4		
URI	Upper respiratory tract infection	%	10.6	10.4		
UTI	Urinary tract infection	%	5.7	5.1		
Dyspnea	Dyspnoea	%	5.3	1.2		

Abbreviations: ALT= Alanine aminotransferase, ARR= annualised relapse rate, CUAL= Combined unique active lesion, EOS= end of study, CDA=confirmed disability accumulation, FSIQ-RMS= Fatigue Symptoms and Impacts Questionnaire – Relapsing Multiple Sclerosis

99% CI is presented according to the applicant's approach. 95% CI is available, and it may be considered more appropriate to present this in the final report to enable comparison between products

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Ponesimod demonstrated superiority of teriflunomide in ARR. The strength of evidence is strong, as the primary null hypothesis was tested with a two-sided alpha level of 1%, as recommended by CHMP in SA.

As preventing relapses is an accepted treatment goal of DMT for MS, ponesimod addresses this goal effectively. The requirements for a single pivotal trial are mostly met. The study population is representative of the target population; thus, external validity is fulfilled. The effect size is clinically relevant and clearly statistically significant. The effect was in general consistent across subgroups; thus, internal consistency is fulfilled. A clear superiority of ponesimod over teriflunomide was demonstrated in MRI outcomes, including CUALs.

A limited number of patients with SPMS was included in the study. However, as efficacy in relapses can be extrapolated from RRMS to SPMS, the indication RMS would in principle be acceptable.

Ponesimod failed to show superiority to teriflunomide in disability progression. It is noted that not demonstrating statistically significant differences in disability progression vs. another DMT is not unusual in RMS studies, considering the current, low relapse rates and slow disability progression in general in RMS population included in clinical studies.

Fatigue is considered a relevant outcome to examine in a clinical study in patients with MS. The applicant developed a patient-reported outcome to assess MS-associated fatigue, and a statistically significant difference in favour of ponesimod was demonstrated in the pivotal study, which was seen at week 60 of treatment. However, the difference between the groups, or the change from baseline, is not considered clinically relevant. Moreover, there was no improvement from baseline in fatigue score under ponesimod treatment. There was a worsening in fatigue score in the teriflunomide arm. The statistically significant difference was due to a worsening in the control arm. This is not unexpected due to the fact that in the control arm more relapses occurred with persisting symptoms contributing to the fatigue. Thus ponesimod has not demonstrated a positive effect on fatigue, which is a debilitating symptom in many patients with MS.

The safety profile is in line with that known for S1P modulators, i.e. having a bradyarrhythmia at first doses, the risk for malignancies, macular oedema, hepatotoxicity and respiratory impairment (dyspnoea). Bradyarrhythmia was no longer reported following the proposed careful up-titration regimen in patients with a HR >55 bpm. Moreover, the evaluation of risk factors for symptomatic bradyarrhythmia will be done in all patients before initiation of ponesimod treatment. Recommendations are included in section 4.4 of the SmPC. These are consistent with the label recommendations of other S1P modulators.

The AEs malignancies, macular oedema, hepatotoxicity and respiratory impairment can be severe in nature and do not resolve on their own. However, these AEs can be monitored and managed. For the RRMS population, these AEs are considered acceptable for other S1P modulators. Moreover, the use of the non-selective S1P modulator in the market for more than 9 years proved that the risk minimisation measures are efficacious. The safety issues are, therefore considered manageable and do not preclude a positive benefit-risk.

AEs in the SOC reproductive system and breast disorders are anticipated based on non-clinical data, mechanistic data and findings in products of the same class. Relevant statements are included in the SmPC; active monitoring in the PSUR is not considered necessary.

There is no experience in the elderly population, however, the popPK modelling did not identify any specific age-related safety issues. Therefore the post marketing follow up in the PSUR is considered adequate.

3.7.2. Balance of benefits and risks

Ponesimod clearly demonstrated superiority to teriflunomide in relapse rate and MRI outcomes in patients with RMS. Based on these data, ponesimod offers an effective alternative for the treatment of RMS.

The safety profile of ponesimod is well known, can be monitored and has been accepted for other S1P modulators. Therefore, the safety concerns raised do not preclude a positive B/R.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable

3.8. Conclusions

The overall B/R of Ponvory is positive.

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 Ponvory is favourable in the following indication:

> *Ponvory is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features.*

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 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

An educational material for healthcare professionals to address the risk(s) of

- Bradyarrhythmia occurring post-first dose
- Macular oedema
- Bronchoconstriction
- Severe liver injury
- Serious opportunistic infections including PML
- Skin cancer
- Reproductive and embryofoetal toxicity
- Convulsions
- Unexpected neurological or psychiatric symptoms/signs (PRES, ADEM, atypical MS relapses)

An educational material for patients and/or carers to address the risk(s) of

- Bradyarrhythmia occurring post-first dose
- Macular oedema
- Bronchoconstriction
- Severe liver injury
- Serious opportunistic infections including PML
- Skin cancer
- Reproductive and embryofoetal toxicity
- Convulsions
- Unexpected neurological or psychiatric symptoms/signs (PRES, ADEM, atypical MS relapses)

A patient alert card to address the risk(s) of

- Reproductive and embryofoetal toxicity

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that ponesimod is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.