European Union Risk Management Plan
Ponvory (Ponesimod)

Data lock point for current RMP	31 March 2023	Version number	3.1

QPPV Sign-off Date: 26 February 2024
RMP Version Number: 3.1
Supersedes Version: 2.1
EDMS Number: EDMS-ERI-184593990, 8.0

QPPV Name(s):	Dr. Laurence Oster-Gozet, PharmD, PhD
QPPV Signature:	The MAH QPPV has either reviewed and approved this RMP, or approved with an electronic signature appended to this RMP, as applicable.

Details of this RMP Submission	
Version Number	3.1
Rationale for submitting an updated RMP (if applicable)	To revise milestones for the category 3 additional pharmacovigilance activity, Survey to Assess the Effectiveness of Ponvory Educational Materials for Additional Risk Minimization Measures in the European Union. To revise milestones for the category 3 additional pharmacovigilance activity, Ponesimod Pregnancy Outcomes Program Utilizing Enhanced Pharmacovigilance Monitoring, as agreed with the PRAC in Procedure No. EMEA/H/C/005163/MEA/001.4.
Summary of significant changes in this RMP	Parts III.2, III.3, V.3, VI II.B, VI II.C.2, Annex 2: • Revised milestones (start of data collection, end of data collection, interim report, and final report) for the category 3 additional pharmacovigilance activity, PCSNSP003693: Survey to Assess the Effectiveness of Ponvory Educational Materials for Additional Risk Minimization Measures in the European Union. • Revised milestones (interim reports) for the category 3 additional pharmacovigilance activity, PCSNSP004001: Ponesimod Pregnancy Outcomes Program Utilizing Enhanced Pharmacovigilance Monitoring (POEM). Annex 3 • Removal of synopses

Other RMP Versions Under Evaluation:

RMP Version Number	Submitted on	Procedure Number
Not applicable		

Details of the Currently Approved RMP:

Version number of last agreed RMP	2.1
Approved within procedure	EMEA/H/C/005163/IB/0012
Date of approval (Competent authority opinion date)	28 July 2023 (CHMP Opinion)

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PART I: PRODUCT(S) OVERVIEW

Active substance(s) **(international nonproprietary name [INN] or common name)**	Ponesimod
Pharmacotherapeutic group(s) (Anatomical Therapeutic Chemical [ATC] Code)	Immunosuppressants, selective immunosuppressants (L04AA50)
Marketing Authorization Holder (MAH)	Janssen-Cilag International, NV
Medicinal products to which the Risk Management Plan (RMP) refers	1
Invented name(s) in the European Economic Area (EEA)	Ponvory
Marketing authorization procedure	Centralized
Brief description of the product	**Chemical class:** Ponesimod is an iminothiazolidinone derivative and a selective sphingosine-1-phosphate receptor 1 ($S1P_1$) modulator.
	Summary of mode of action: Ponesimod binds with high affinity to $S1P_1$ located on lymphocytes. Ponesimod blocks the capacity of lymphocytes to egress from lymph nodes reducing the number of lymphocytes in peripheral blood. The mechanism by which ponesimod exerts therapeutic effects in multiple sclerosis (MS) may involve reduction of lymphocyte migration into the central nervous system (CNS).
	Important information about its composition: Not applicable
Reference to the Product Information	Module 1.3.1, Summary of Product Characteristics, Labeling and Package Leaflet
Indication(s) in the EEA	**Current:** Ponesimod is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features.
	Proposed: Not applicable

<table>
<tr><td rowspan="2">Dosage in the EEA</td><td colspan="2">Current:
Treatment with ponesimod must be started with the 14-day treatment initiation pack. Treatment starts with one 2-mg tablet orally once daily on Day 1 and dose escalation progresses with the titration schedule outlined in the following table:
<table><tr><th>Titration day</th><th>Daily dose</th></tr><tr><td>Days 1 and 2</td><td>2 mg</td></tr><tr><td>Days 3 and 4</td><td>3 mg</td></tr><tr><td>Days 5 and 6</td><td>4 mg</td></tr><tr><td>Day 7</td><td>5 mg</td></tr><tr><td>Day 8</td><td>6 mg</td></tr><tr><td>Day 9</td><td>7 mg</td></tr><tr><td>Day 10</td><td>8 mg</td></tr><tr><td>Day 11</td><td>9 mg</td></tr><tr><td>Days 12, 13, and 14</td><td>10 mg</td></tr></table>After dose titration is complete, the recommended maintenance dose of ponesimod is one 20-mg tablet taken orally once daily.</td></tr>
<tr><td colspan="2">Proposed: Not applicable</td></tr>
<tr><td rowspan="2">Pharmaceutical form(s) and strengths</td><td colspan="2">Current:
Ponesimod is formulated as round, biconvex, film-coated tablets for oral use.
The following tablet strengths are available: 2, 3, 4, 5, 6, 7, 8, 9, 10, and 20 mg.</td></tr>
<tr><td colspan="2">Proposed: Not applicable</td></tr>
<tr><td>Is/will the product be subject to additional monitoring in the European Union (EU)?</td><td>☑ Yes</td><td>☐ No</td></tr>
</table>

PART II: SAFETY SPECIFICATION

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

Indication: Relapsing Forms of Multiple Sclerosis

Incidence:

According to the Global Burden of Disease Study, there were approximately 69,000 incident cases of MS in 2016 (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators 2017). At the time of diagnosis, 85% of the patients had relapsing-remitting multiple sclerosis (RRMS). According to the MS International Federation, it has been estimated that up to 80% of these patients will go on to develop secondary progressive MS. In 2020, the median incidence was estimated to be 2.1 per 100,000 population globally, and 6.8 per 100,000 population in Europe. The table below shows the incidence of MS in selected European countries for 2020 (MS International Federation 2020).

Country	Incidence of MS per 100,000 population
Austria	19.5
Belgium	4.3
Denmark	10.4
Finland	5.8
France	6.2
Germany	17.6
Greece	5.7
Hungary	data not known
Netherlands	9.0
Norway	data not known
Poland	4.5
Portugal	3.1
Spain	4.2
Sweden	8.7
Switzerland	data not known
United Kingdom	10.0

Prevalence:

Globally, the prevalence of MS in 2016 was estimated to be 30.1 cases per 100,000 population (95% uncertainty interval [UI]: 27.5-33.0) (GBD 2016 Multiple Sclerosis Collaborators 2019). In 2020, the median prevalence was estimated to be 36 per 100,000 population globally, and 133 per 100,000 population in Europe. The table below shows the prevalence of MS in selected European countries for 2020 (MS International Federation 2020).

Country	Prevalence of MS per 100,000 population
Austria	153
Belgium	104
Denmark	282
Finland	218
France	155
Germany	303
Greece	124
Hungary	90
Netherlands	150
Norway	data not known
Poland	120
Portugal	56
Spain	120
Sweden	218
Switzerland	180
United Kingdom	196

Demographics of the Population in the Authorized Indication - Age, Sex, Racial and/or Ethnic Origin, Geographic Distribution, and Risk Factors for the Disease

Age

In general, the incidence of MS peaks at about 30 years of age, and prevalence peaks at about 50 years of age (Koch-Henriksen 2010). In 2020, the average age of onset worldwide was approximately 32 years, and in Europe, it was approximately 33 years, varying from 20 years in Estonia to 40 years in Finland (MS International Federation 2020).

Sex

In many regions, MS is more common in women than in men, with the female-to-male ratio varying between 1.5:1 and 2.5:1 (Ascherio 2016). In Europe, in 2020, the female-to-male ratio was estimated to be 2.2, ranging from 1.1:1 in Latvia to 3.8:1 in Portugal (MS International Federation 2020). According to data from the Lyon MS database collected by the European Database for Multiple Sclerosis system, there has been an increasing incidence of MS in women, with one study showing the female-to-male ratio increasing from 1.68:1 in 1960 to 2.45:1 in 2005 (Leray 2016).

Ethnicity

White people, particularly those of Northern European descent, are at the highest risk of developing MS. People of Asian, African, or Native American descent have the lowest risk (Mayo Clinic 2020).

Geographic Distribution

There is evidence to suggest a strong latitude gradient for the prevalence of MS, with an increase in prevalence from the equator to the poles but this effect may be attenuating (Ascherio 2016). In 2016, prevalence was the highest in North America (164.6 per 100,000 population, 95% UI: 153.2-177.1), and Western Europe (127.0 per 100,000 population, 95% UI: 115.4-139.6). Prevalence was the lowest in Eastern sub-Saharan Africa (3.3 per 100,000 population, 95% UI: 2.9-3.8), Central sub-Saharan Africa (2.8 per 100,000 population, 95% UI: 2.4-3.1), and Oceania (2.0 per 100,000 population, 95% UI: 1.71-2.29) (GBD 2016 Multiple Sclerosis Collaborators 2019).

Risk Factors for the Disease

Environmental risk factors for MS include a history of Epstein-Barr virus (EBV) infection, infectious mononucleosis, and smoking, with EBV being the strongest risk factor (Leray 2016). There is evidence to suggest that vitamin D deficiency and obesity early in life may also be risk factors for MS (Ascherio 2016). Genetic susceptibility is also a determining factor of MS, but the contribution of any specific gene seems to be modest (Goodin 2016).

Main Existing Treatment Options:

The treatment of MS falls into 3 categories: treatment of exacerbations, slowing disease progression with disease-modifying therapies (DMTs), and symptomatic therapies (Hart 2016).

Treatment for MS exacerbations include corticosteroids, such as prednisone and methylprednisolone, to reduce nerve inflammation, and plasma exchange (Hart 2016).

There are currently more than a dozen approved DMTs for MS with different efficacy and safety profiles. DMTs work by controlling, segregating, blocking, or depleting disease-causing autoimmune cells, thus limiting their ability to enter and damage the CNS (Freedman 2016), with the goal to reduce disease activity that contributes to long-term disability (Hart 2016). The injectable interferons (interferons β-1a and β-1b) and glatiramer acetate are relatively safe but only provide moderate control of the disease. Oral therapies have a higher effect on the reduction of relapses but have safety, tolerability, or pharmacokinetic (PK) issues, including slow PK/pharmacodynamic (PD) reversibility and high propensity for drug-drug interactions, as well as complexities related to metabolism, requiring genotyping. Oral medications currently approved in the European Union (EU) include fingolimod, siponimod, ozanimod, dimethyl fumarate, cladribine, and teriflunomide (European Medicines Agency [EMA] 2020). These oral medications are associated with safety concerns of cardiac, macular edema (for sphingosine-1-phosphate [S1P] receptor modulators), flushing and gastrointestinal side effects (for dimethyl fumarate), and alopecia (for teriflunomide). The most efficacious DMTs are monoclonal antibodies such as natalizumab, alemtuzumab, ocrelizumab, and ofatumumab, but they may have safety concerns, including the risk of progressive multifocal leukoencephalopathy (PML), autoimmune disease, and malignancies.

Symptomatic therapies include muscle relaxants, medications to reduce fatigue such as amantadine and modafinil, medications to improve walking such as dalfampridine or fampridine, and physical therapy (Hart 2016, EMA 2020).

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity:

MS is an unpredictable disease of the CNS and can range from relatively benign to somewhat disabling to devastating, as communication between the brain and other parts of the body is disrupted (NINDS 2019). It is an autoimmune disorder and the duration of the disease can span 4 to 5 decades (Ebers 2001). Most patients with MS have a relapsing-remitting disease course, which involves periods of new symptoms or relapses with exacerbations of previous symptoms that usually improve partially or completely. These relapses are followed by quiet periods of disease remission that can last months (Files 2015). RRMS usually progresses to secondary progressive disease within 15 to 20 years (Faissner 2018). Only 10% to 15% of patients initially present with primary progressive disease (Faissner 2018).

MS is a heterogeneous condition in terms of the presentation of symptoms and the response to therapy (Lemus 2018). The majority of patients experience some degree of impairment immediately after disease onset, with sensory symptoms and fatigue being common. As the disease progresses, patients can experience mild to moderate cognitive impairment and mobility is also affected (Kister 2013). In relapsing-onset MS, the presence of a residual deficit after the first relapse and the occurrence of relapses during the first 2 or 5 years of MS significantly influences disability progression, with symptoms becoming more pronounced after each relapse (Leray 2016). One study conducted in France reported that the median time to moderate disability from the clinical onset of MS was 7.4 years, and 7 years from moderate disability to more severe disability (defined as needing assistance to walk 100 meters) (Leray 2010).

Mortality

Globally, there were 18,932 deaths due to MS (95% UI: 16,577-21,033) in 2016, which represents an 11.5% reduction in the age-standardized mortality rate since 1990. In Western Europe, there were 4,795 deaths due to MS in 2016, which represents a reduction of 2.1% since 1990 (GBD 2016 Multiple Sclerosis Collaborators 2019). Excess mortality in MS patients has been demonstrated in several studies, with life expectancy reduced by 6 to 14 years and 50% to 70% of deaths considered MS-related, with MS being either the main cause or a contributing cause (Leray 2016).

Important Comorbidities:

Important comorbidities associated with MS include autoimmune disorders, such as ulcerative colitis, regional enteritis, and thyroid gland disorders; ischemic stroke; myocardial infarction; sepsis; opportunistic infections; urinary tract infections; depression; anxiety; lymphoproliferative disorder; melanoma; hypertension; hyperlipidemia; chronic lung disease; diabetes; and uveitis (Marrie 2015, Marrie 2016, Capkun 2015).

PART II: SAFETY SPECIFICATION

Module SII: Nonclinical Part of the Safety Specification

Key Safety Findings	Relevance to Human Usage
Toxicity	
Repeat-dose toxicity	
Repeat-dose oral toxicity studies of up to 3, 6, and 12 months duration in the mouse, rat, and dog, respectively, were conducted with ponesimod. The no-observed-adverse-effect level (NOAEL) of 3 mg/kg/day was established in the 52-week repeat-dose toxicity study in the dog and was defined by the absence of histopathological findings in the heart. When compared with human systemic exposures at the recommended human dose (RHD) of 20 mg/day, the NOAEL in the dog is 4.3 and 6.2 times the human systemic exposures based on the area under the concentration-time curve from time 0 to 24 hours ($AUC_{0–24}$) and maximum concentration (C_{max}), respectively.	
Toxicity studies in mice, rats, and dogs identified toxicities in the following target organs:	
Heart. Coronary arterial lesions within papillary muscles of the left ventricle were noted in dogs after 13 to 52 weeks of ponesimod treatment. The arterial lesions did not worsen and did not induce secondary adverse changes in the heart after chronic treatment. These lesions are considered secondary to hemodynamic changes (specifically, arterial vasoconstriction, blood pressure increase, and increased perfusion pressure in the left papillary muscles). The selective development of cardiac lesions in the left papillary muscles was caused by sphingosine-1-phosphate receptor 3 ($S1P_3$)-mediated vasoconstriction, with secondary hemodynamic and cellular changes.	Nonclinical data do not indicate a safety concern for humans at the RHD of 20 mg/day. The hemodynamic changes and the arterial lesions were only observed in the dog, a species that is known to be particularly sensitive to hemodynamic changes in the heart and their associated toxicity. The hemodynamic changes were demonstrated to be $S1P_3$ mediated, and in vitro studies demonstrated higher levels of $S1P_3$ in the coronary arteries of dogs versus humans, which would result in an additional pharmacological sensitivity in the dog. Taking into account the toxicological and mechanistic characterization of the arterial lesion in the left papillary muscle of dogs, these lesions would not be expected in humans following chronic administration at the RHD of 20 mg/day.

Key Safety Findings	Relevance to Human Usage
Lung. A transient adaptive pulmonary histiocytosis secondary to perivascular edema was noted in mice, rats, and dogs. Alveolar histiocytosis is not considered a serious pathological change and represents a clearing process within the lung. It is often a background finding in experimental animals. The severity of the finding in animals was dose-dependent in all species. The histiocytosis was of low incidence (dogs) or was not detected (rats) in the subchronic and chronic studies; therefore, it can be considered as a transient and spontaneously reversible phenomenon, confirming its role in fluid clearance. This process of adaptation was also observed in mice with findings after 14 days of treatment and complete disappearance of the findings after 13 weeks of treatment. Assessment of lung function by plethysmography after single exposure in rats and dogs and after 4-week exposure in rats did not indicate adverse functional changes in the lung. There was no consistent link between histiocytosis and lung function in animals, and the effects resolved or were less pronounced in all 3 species after prolonged treatment.	Nonclinical data do not indicate a safety concern for humans. Vascular permeability changes are $S1P_1$ mediated, and these pulmonary findings may be expected to occur in humans. However, they are considered transient and adaptive changes and did not result in a functional change in the pulmonary system of rats or dogs.
Nervous system. In the dog, clinical observations of tremor, recumbency, muscle twitching, uncoordinated movements, decreased activity, and buckling of the hind limbs were noted at doses of ≥75 mg/kg/day. Detailed neurological examinations and histology in 4- to 52-week dog studies showed no effects. The rat and mouse toxicity studies, as well as the rat Irwin test, showed no evidence of central and/or peripheral nervous system-related effects.	Nonclinical data do not indicate a safety concern for humans. These findings were noted only in the dog, and subsequent detailed neurological examinations in the dog revealed no further findings. A NOAEL established in a 26-week dog study provides safety margins of 32- to 44-fold the clinical C_{max} at the RHD of 20 mg/day. The systemic exposure required to cause these effects in dogs is significantly higher than the clinical exposure at the RHD; therefore, these effects are not considered clinically relevant.
Lymphatic system. Lymphopenia and lymphoid atrophy were noted in all species. These are considered PD effects.	These changes are a direct consequence of primary pharmacology (lymphocyte sequestration) and the observed effects are reversible in animals. Clinical trials indicate that lymphocyte counts return to base values after ponesimod treatment discontinuation.

Key Safety Findings	Relevance to Human Usage
Adrenals and lipids. In the rat, increased incidence of fatty change in the adrenal cortex and increased blood lipids were noted. The incidence of fatty change in the adrenal cortex was increased in the 14-day rat study at all doses (≥30 mg/kg/day). In the 4-week study, the finding occurred only at 100 mg/kg/day (and not at 30 mg/kg/day), and in the 26-week study, it was not observed at any dose level up to 100 mg/kg/day, suggesting some processes of adaptation with longer treatment. These findings may be related to increased plasma lipids (low density lipoprotein- and high density lipoprotein-cholesterol, triglycerides) noted in the rat and the dog (adrenal changes were not noted in the dog). These changes are considered to be of limited toxicological relevance.	Nonclinical data do not indicate a safety concern for humans. Adrenal changes occurred only in the rat. These findings, in addition to the lipid changes, are considered a non-adverse metabolic adaptation and of no concern to humans.
Skin. In the dog, an increased incidence of skin lesions (eg, alopecia, nodules, sores, and eschar, mainly on the legs/paws) was noted in 13- to 52-week studies and was also seen histologically as increased incidence of dermatitis and folliculitis, associated sometimes with granulomas, acanthosis, and hyperkeratosis. These findings are an exacerbation of common background findings in dogs and are possibly linked to immunomodulatory pharmacology of ponesimod.	Nonclinical data do not indicate a safety concern for humans. These findings are an exacerbation of common skin lesions found in healthy dogs. As these skin lesions do not normally occur in humans, these are not considered clinically relevant.
Reproductive toxicity	
In the male and female fertility studies in rats, mating and fertility were unaffected by treatment at doses up to 100 mg/kg/day. There was no effect on early pregnancy or sperm parameters. No effects were observed on male reproductive organs when evaluated histopathologically in repeat-dose toxicology studies of up to 26 or 52 weeks duration in rats or dogs, respectively.	Nonclinical data suggest that ponesimod is unlikely to have an adverse effect on fertility in humans.

Key Safety Findings	Relevance to Human Usage
Developmental toxicity	
When ponesimod was orally administered (1, 10, or 40 mg/kg/day) to pregnant rats during the period of organogenesis, embryofetal survival, growth, and morphological development were severely compromised at doses ≥40 mg/kg/day. Teratogenic effects with major skeletal and visceral abnormalities were observed at doses ≥10 mg/kg/day. A NOAEL for embryofetal developmental toxicity in rats was established at 1 mg/kg/day. When ponesimod was orally administered (0.25, 1, or 4 mg/kg/day) to pregnant rabbits during the period of organogenesis, a slight increase in postimplantation losses and fetal findings (visceral and skeletal) were noted at 4 mg/kg/day. The embryofetal NOAEL in rabbits was 1 mg/kg/day. The C_{max} and AUC_{0-24} in rats and rabbits at the NOAEL of 1 mg/kg/day (both species) are lower than the human systemic exposures at the RHD of 20 mg/day. When ponesimod was orally administered (5, 10, or 20 mg/kg/day) to female rats throughout pregnancy and lactation, decreased pup survival, decreased body weight gain, and reduced fertility (females only) were observed in the offspring at 20 mg/kg/day only. All ponesimod-treated F1 pups had delayed sexual maturation. Plasma exposure (AUC_{0-24}) at the NOAEL of 10 mg/kg/day is 1.2 to 1.5 times that in humans at the RHD of 20 mg/day. F1 pups were also noted to have ponesimod in the plasma on lactation days 4 and 12, which indicates ponesimod exposure to pups via the milk of lactating dams.	Nonclinical data indicate a relevant safety concern in humans. The biology of the pharmacological target $S1P_1$ is known to involve cell migration and angiogenesis. Thus, the teratogenicity seen in rats and rabbits following ponesimod exposure is considered a relevant safety concern in humans. Reproductive and embryofetal toxicity is considered an important potential risk for ponesimod. Data indicate ponesimod exposure to pups via the milk of lactating dams; therefore, exposure to human infants via the milk of breast-feeding women can be expected.
Genotoxicity	
Ponesimod has no genotoxic potential, as evidenced in the in vitro bacterial reverse mutation (Ames) assay, the chromosome aberration test, and the in vivo rat micronucleus test. Metabolites M13 and M12 were not mutagenic in the Ames test.	Nonclinical data do not indicate a safety concern for humans.

Key Safety Findings	Relevance to Human Usage
Carcinogenicity	
Oral carcinogenicity studies of ponesimod were conducted in mice and rats. Ponesimod did not induce neoplastic lesions in rats following administration for up to 2 years. In mice, ponesimod was administered at oral doses of 50, 150, and 400 mg/kg/day in males and 30, 100, and 300 mg/kg/day in females for up to 2 years. The combined total incidence of hemangiosarcoma and hemangioma was significantly increased in all treated males and females treated at or above 300 mg/kg/day.	Mouse hemangiosarcoma and hemangioma have been reported for other $S1P_1$ modulators and are possibly a species-specific effect caused by a combination of $S1P_1$-mediated effects and a higher rate of vascular endothelial cell turnover in mice when compared with rats and humans. The lowest dose tested in female mice is the no-observed-effect level for carcinogenesis, and the AUC_{0-24} is 2.4-fold the human systemic exposure at the RHD of 20 mg.
Safety pharmacology:	
Cardiovascular system (including potential for QT interval prolongation)	
No in vitro or in vivo (in dogs and guinea pigs) QT prolongation effects were noted following ponesimod exposure. In guinea pigs, single doses of ponesimod ≥0.3 mg/kg/day induced atrioventricular (AV) blocks and decreased heart rate (HR). These cardiovascular effects were significantly reduced on repeated dosing and after a low starting dose and up-titration (desensitization). Increases in blood pressure were noted in dogs following single and repeated dosing and in rats following repeated dosing only (28-day repeated dosing study in normotensive rats).	Nonclinical data do not indicate any QT prolongation-related safety concern for humans. AV block and decreased HR are known clinical effects of S1P receptor modulators. Up-titration has successfully been used in ponesimod clinical trials to reduce effects on HR and conductance delays. Bradyarrhythmia occurring post-first dose is considered an important identified risk for ponesimod. Blood pressure increases in dogs were demonstrated to be $S1P_3$-mediated, and in vitro studies demonstrated higher levels of $S1P_3$ in the arteries of dogs versus humans, resulting in a pharmacologically higher sensitivity in dogs compared to humans. Increased blood pressure was noted following repeated dosing in rats and is considered a relevant safety effect in humans. Hypertension has been noted in ponesimod-treated patients. Although it is an identified risk for ponesimod, it is not considered an important risk.

Key Safety Findings	Relevance to Human Usage
Pulmonary function	
Dose- and time-dependent effect on respiratory function was noted in rats but not in dogs. Slight impairment in respiratory function was observed at the start of dosing but resolved completely after 4 weeks of dosing in rats. This functional effect is characterized as a decrease in the relaxation time with a slight increase in the peak expiratory flow and tidal volume (increase in Penh), which indicates a transition from passive to more active expiration.	The pulmonary function effects observed in rats are relevant to humans. In the rat, a mild increase in Penh may reflect an increased bronchial tone during expiration and may potentially mediate dyspnea noted clinically. Dose-dependent reductions in percent predicted forced expiratory volume in 1 second and reductions in diffusion lung capacity for carbon monoxide (assessed only for the ponesimod 20-mg dose level) have been observed during treatment with ponesimod in clinical trials. These reductions mostly occurred in the first month after treatment initiation, remained stable over the duration of treatment, and appeared to be partially reversible upon study treatment discontinuation. Bronchoconstriction is considered an important identified risk for ponesimod.
Hepatotoxicity	
Minor non-adverse changes consisting of increased liver weight (mice, rats, and dogs) and centrilobular hepatocellular hypertrophy (mice and rats) are considered a metabolic adaptation to ponesimod treatment. In mice, diffuse hepatocellular fatty change, glycogen deposition, and increased mitotic activity were noted at 100 mg/kg/day for 14 days but not at ≤90 mg/kg/day for 13 weeks. Hepatocyte vacuolation and coagulative necrosis were seen at ≥400 mg/kg/day for 13 weeks.	Nonclinical data do not indicate a safety concern for humans.
Other toxicity-related information or data	
Effects on kidney and brain in the rat carcinogenicity study	
In a 104-week carcinogenicity study in rats, ponesimod-related effects were noted in the kidney (chronic progressive nephropathy [CPN]) and brain (unilateral focal necrosis) of treated females. CPN is a commonly seen age-related background finding in rats (Hard 2009). The functional and pathological changes associated with CPN are expected to cause blood pressure increase in rats (Hard 2009). Indeed, hypertrophy of the adrenal zona glomerulosa was seen in all treated females, which is known to be	Nonclinical data do not indicate a safety concern for humans. CPN has no direct correlate in humans and is generally considered not relevant to humans. As CPN is an important contributor to the increased blood pressure that resulted in the unilateral focal necrosis observed in the brains of female rats, the brain lesion is not considered relevant to humans.

Key Safety Findings	Relevance to Human Usage
associated with derangements of the renin-angiotensin system that result in elevated angiotensin II, which causes increases in blood pressure. Ponesimod is also reported to cause vasoconstriction and increased blood pressure. These multifactorial vascular components are considered to cause localized ischemic conditions that have the potential to result in the unilateral focal necrosis in the brain (Kaufmann 2012, Kalaria 2015, Meyer 1960, Phillips 1994).	

Summary of Nonclinical Safety Concerns

Important identified risks	Bradyarrhythmia occurring post-first dose
	Bronchoconstriction
Important potential risks	Reproductive and embryofetal toxicity
Missing information	None

PART II: SAFETY SPECIFICATION

Module SIII: Clinical Trial Exposure

SIII.1. Brief Overview of Development

Ponesimod is being developed for the treatment of adult patients with RMS.

Data from the following clinical trials are included in this European Union Risk Management Plan (EU-RMP):

- **Completed Phase 3 Trial AC-058B301/OPTIMUM** (pivotal trial; further referred to as B301) was a multicenter, randomized, double-blind, parallel-group, active-controlled superiority trial to compare the efficacy, safety, and tolerability of ponesimod 20 mg to teriflunomide 14 mg administered for 108 weeks in subjects with RMS.
- **Ongoing Phase 3 Trial AC-058B303/OPTIMUM-LT** (supportive trial; further referred to as B303) is a multicenter, open-label, non-comparative, long-term extension to Trial B301 to investigate the long-term safety, tolerability, and control of disease of ponesimod 20 mg administered up to 240 weeks in subjects with RMS.
- **Completed Phase 2b Trial AC-058B201** (supportive trial; further referred to as B201) was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-finding trial to evaluate the efficacy, safety, and tolerability of 3 doses of ponesimod (10, 20, 40 mg) versus placebo, administered for 24 weeks in subjects with RRMS.
- **Ongoing Phase 2b Trial AC-058B202** (supportive trial; further referred to as B202) is a multicenter, randomized, double-blind, uncontrolled, parallel-group extension to Trial B201 to investigate the long-term safety, tolerability, and efficacy of 3 doses of ponesimod (10, 20, 40 mg) in subjects with RRMS. The 10- and 20-mg doses are administered up to 636 weeks and the 40-mg dose up to 96 weeks.

SIII.2. Clinical Trial Exposure

Exposure in Randomized, Double-blind Clinical Trials

The randomized, double-blind, active- or placebo-controlled clinical trials population includes 2 trials:

- Trial B201 (24-week double-blind placebo control phase)
- Trial B301 (108-week double-blind active control phase, exposure up to 24 weeks)

Exposure to ponesimod in the All Randomized Double-blind (RDB) Clinical Trials Population is summarized in Tables SIII.1 through SIII.6 for all subjects by duration, by age group and sex, by dose, by maximum dose, by dose sequence received, and by race.

Table SIII.1: Clinical Trial Exposure[1] to Ponesimod (24 Weeks) in All Randomized Double-blind Trials[2] by Duration of Exposure

INDICATION: Multiple Sclerosis		
Duration of exposure[2]	**Patients**	**Patient-years**
≥1 day	906	409.6
≥4 weeks	873	408.6
≥12 weeks	834	403.2
≥24 weeks	699	345.6

1 Irrespective of study treatment interruptions.
2 Trials included in the All Randomized Double-blind (RDB) Clinical Trials Population are AC-058B201 (24-week double-blind placebo control phase) and AC-058B301 (108-week double-blind active control phase, exposure up to 24 weeks).

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Table SIII.2: Clinical Trial Exposure[1] to Ponesimod (24 Weeks) in All Randomized Double-blind Trials[2] by Age Group and Sex

INDICATION: Multiple Sclerosis						
	Men		**Women**		**All**	
Age group	**Patients**	**Patient-years**	**Patients**	**Patient-years**	**Patients**	**Patient-years**
<18 years	0	0.0	0	0.0	0	0.0
18-30 years	92	43.0	157	71.3	249	114.2
31-40 years	132	58.6	222	99.9	354	158.5
41-55 years	92	42.8	211	94.0	303	136.9
>55 years	0	0.0	0	0.0	0	0.0
All patients	316	144.4	590	265.2	906	409.6

1 Irrespective of study treatment interruptions.
2 Trials included in the All Randomized Double-blind (RDB) Clinical Trials Population are AC-058B201 (24-week double-blind placebo control phase) and AC-058B301 (108-week double-blind active control phase, exposure up to 24 weeks).

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Table SIII.3: Clinical Trial Exposure[1] to Ponesimod (24 Weeks) in All Randomized Double-blind Trials[2] by Dose[3]

INDICATION: Multiple Sclerosis		
Dose of exposure[4]	**Patients**	**Patient-years**
Ponesimod 2 mg	565	3.2
Ponesimod 3 mg	563	3.2
Ponesimod 4 mg	563	3.3
Ponesimod 5 mg	562	1.6
Ponesimod 6 mg	562	1.6
Ponesimod 7 mg	561	1.6
Ponesimod 8 mg	561	1.6
Ponesimod 9 mg	561	1.6
Ponesimod 10 mg	902	53.9
Ponesimod 20 mg	785	295.6
Ponesimod 40 mg	115	42.1
Any ponesimod dose	906	409.6

1 Irrespective of study treatment interruptions.
2 Trials included in the All Randomized Double-blind (RDB) Clinical Trials Population are AC-058B201 (24-week double-blind placebo control phase) and AC-058B301 (108-week double-blind active control phase, exposure up to 24 weeks).
3 Ponesimod doses received at any time by a subject ie, during up-titration (first dose or at re-initiation) or double-blind phase.

Table SIII.3: Clinical Trial Exposure[1] to Ponesimod (24 Weeks) in All Randomized Double-blind Trials[2] by Dose[3]

INDICATION: Multiple Sclerosis		
Dose of exposure[4]	**Patients**	**Patient-years**

[4] Multiple doses per subject are considered. A subject is counted in each of the dose categories if (s)he received at least one dose within that category.

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Table SIII.4: Clinical Trial Exposure[1] to Ponesimod (24 Weeks) in All Randomized Double-blind Trials[2] by Maximum Dose[3]

INDICATION: Multiple Sclerosis		
Dose of exposure	**Patients**	**Patient-years**
Ponesimod 2 mg	1	0.0
Ponesimod 3 mg	0	0.0
Ponesimod 4 mg	0	0.0
Ponesimod 5 mg	1	0.0
Ponesimod 6 mg	1	0.0
Ponesimod 7 mg	0	0.0
Ponesimod 8 mg	0	0.0
Ponesimod 9 mg	0	0.0
Ponesimod 10 mg	118	44.5
Ponesimod 20 mg	670	293.4
Ponesimod 40 mg	115	42.1
Any ponesimod dose	906	409.6

[1] Irrespective of study treatment interruptions.
[2] Trials included in the All Randomized Double-blind (RDB) Clinical Trials Population are AC-058B201 (24-week double-blind placebo control phase) and AC-058B301 (108-week double-blind active control phase, exposure up to 24 weeks).
[3] Ponesimod maximum dose received at any time by a subject. A subject is counted only in one dose category.

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Table SIII.5: Clinical Trial Exposure[1] to Ponesimod (24 Weeks) in All Randomized Double-blind Trials[2] by Dose Sequence Received[3]

INDICATION: Multiple Sclerosis		
Dose of exposure[4]	**Patients**	**Patient-years**
Ponesimod 2/3/4/5/6/7/8/9/10/20 mg sequence	541	262.5
Ponesimod 2/3/4/5/6/7/8/9/10/20 mg repeated sequence	8	3.4
Ponesimod 10 mg	115	44.5
Ponesimod 10/20 mg sequence	110	46.9
Ponesimod 10/20 mg repeated sequence	0	0.0
Ponesimod 10/20/40 mg sequence	111	44.8
Ponesimod 10/20/40 mg repeated sequence	3	1.4
Missing doses in the sequence or any other sequence (partial, reversed, mixed)	18	6.1
Any dose sequence	906	409.6

[1] Irrespective of study treatment interruptions.
[2] Trials included in the All Randomized Double-blind (RDB) Clinical Trials Population are AC-058B201 (24-week double-blind placebo control phase) and AC-058B301 (108-week double-blind active control phase, exposure up to 24 weeks).
[3] Ponesimod doses received at any time by a subject ie, during up-titration (first dose or at re-initiation) or double-blind phase.
[4] A subject is counted in the dose sequence if (s)he received all doses indicated within the sequence during initial up-titration and maintenance.

Table SIII.5: Clinical Trial Exposure[1] to Ponesimod (24 Weeks) in All Randomized Double-blind Trials[2] by Dose Sequence Received[3]

INDICATION: Multiple Sclerosis		
Dose of exposure[4]	**Patients**	**Patient-years**

All doses received including doses received during re-initiation are considered for the patients-year calculation.
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Table SIII.6: Clinical Trial Exposure[1] to Ponesimod (24 Weeks) in All Randomized Double-blind Trials[2] by Race

INDICATION: Multiple Sclerosis		
Race	**Patients**	**Patient-years**
White	880	397.5
Black	9	4.3
Asian	2	1.0
Other[3]	15	6.9
All patients	906	409.6

1 Irrespective of study treatment interruptions.
2 Trials included in the All Randomized Double-blind (RDB) Clinical Trials Population are AC-058B201 (24-week double-blind placebo control phase) and AC-058B301 (108-week double-blind active control phase, exposure up to 24 weeks).
3 Other includes Hispanic, American Indian or Alaska native, Native Hawaiian or Other Pacific Islander, Not applicable, Multiple, Not reported, Other, Unknown.

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Exposure in Randomized Clinical Trials

The All Randomized (R) Clinical Trials Population includes 3 trials:

- Trial B201 (24-week double-blind placebo control phase)
- Trial B202 (initial treatment period [TP] - TP1[1])
- Trial B301 (108-week double-blind active control phase)

Exposure to ponesimod in the R population is summarized in Tables SIII.7 through SIII.12 for all subjects by duration, by age group and sex, by dose, by maximum dose, by dose sequence received, and by race.

1 During TP1, subjects received 10, 20, or 40 mg ponesimod for up to 96 weeks.

Table SIII.7: Clinical Trial Exposure[1] to Ponesimod in All Randomized Trials[2] by Duration of Exposure

INDICATION: Multiple Sclerosis		
Duration of exposure[2]	**Patients**	**Patient-years**
≥1 day	1,000	1,748.9
≥3 months	919	1,741.1
≥6 months	859	1,717.1
≥12 months	831	1,695.6
≥18 months	799	1,654.6
≥24 months	751	1,569.0

1 Irrespective of study treatment interruptions.

2 Trials included in the All Randomized (R) Clinical Trials Population are AC-058B201 (24-week double-blind placebo control phase), AC-058B301 (108-week double-blind active control phase), and AC-058B202 treatment period 1 (TP1).

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Table SIII.8: Clinical Trial Exposure[1] to Ponesimod in All Randomized Trials[2] by Age Group and Sex

INDICATION: Multiple Sclerosis						
	Men		**Women**		**All**	
Age group	**Patients**	**Patient-years**	**Patients**	**Patient-years**	**Patients**	**Patient-years**
<18 years	0	0.0	0	0.0	0	0.0
18-30 years	100	182.0	173	300.6	273	482.6
31-40 years	141	243.5	250	441.6	391	685.1
41-55 years	101	185.1	235	396.1	336	581.2
>55 years	0	0.0	0	0.0	0	0.0
All patients	342	610.7	658	1,138.3	1,000	1,748.9

1 Irrespective of study treatment interruptions.

2 Trials included in the All Randomized (R) Clinical Trials Population are AC-058B201 (24-week double-blind placebo control phase), AC-058B301 (108-week double-blind active control phase), and AC-058B202 treatment period 1 (TP1).

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Table SIII.9: Clinical Trial Exposure[1] to Ponesimod in All Randomized Trials[2] by Dose[3]

INDICATION: Multiple Sclerosis		
Dose of exposure[4]	**Patients**	**Patient-years**
Ponesimod 2 mg	565	3.3
Ponesimod 3 mg	563	3.2
Ponesimod 4 mg	563	3.3
Ponesimod 5 mg	562	1.6
Ponesimod 6 mg	562	1.6
Ponesimod 7 mg	561	1.6
Ponesimod 8 mg	561	1.6
Ponesimod 9 mg	561	1.6
Ponesimod 10 mg	996	251.2
Ponesimod 20 mg	847	1,266.8
Ponesimod 40 mg	147	212.7
Any ponesimod dose	1,000	1,748.9

1 Irrespective of study treatment interruptions.

2 Trials included in the All Randomized (R) Clinical Trials Population are AC-058B201 (24-week double-blind placebo control phase), AC-058B301 (108-week double-blind active control phase), and AC-058B202 treatment period 1 (TP1).

3 Ponesimod doses received at any time by a subject ie, during up-titration (first dose or at re-initiation) or double-blind phase and/or randomized phases (TP1).

Table SIII.9: Clinical Trial Exposure[1] to Ponesimod in All Randomized Trials[2] by Dose[3]

INDICATION: Multiple Sclerosis		
Dose of exposure[4]	**Patients**	**Patient-years**

[4] Multiple doses per subject are considered. A subject is counted in each of the dose categories if (s)he received at least one dose within that category.

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Table SIII.10: Clinical Trial Exposure[1] to Ponesimod in All Randomized Trials[2] by Maximum Dose[3]

INDICATION: Multiple Sclerosis		
Dose of exposure	**Patients**	**Patient-years**
Ponesimod 2 mg	1	0.0
Ponesimod 3 mg	0	0.0
Ponesimod 4 mg	0	0.0
Ponesimod 5 mg	1	0.0
Ponesimod 6 mg	1	0.0
Ponesimod 7 mg	0	0.0
Ponesimod 8 mg	0	0.0
Ponesimod 9 mg	0	0.0
Ponesimod 10 mg	150	240.4
Ponesimod 20 mg	700	1,263.9
Ponesimod 40 mg	147	212.7
Any ponesimod dose	1,000	1,748.9

[1] Irrespective of study treatment interruptions.
[2] Trials included in the All Randomized (R) Clinical Trials Population are AC-058B201 (24-week double-blind placebo control phase), AC-058B301 (108-week double-blind active control phase), and AC-058B202 treatment period 1 (TP1).
[3] Ponesimod maximum dose received at any time by a subject. A subject is counted only in one dose category.

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Table SIII.11: Clinical Trial Exposure[1] to Ponesimod in All Randomized Trials[2] by Dose Sequence Received[3]

INDICATION: Multiple Sclerosis		
Dose of exposure[4]	**Patients**	**Patient-years**
Ponesimod 2/3/4/5/6/7/8/9/10/20 mg sequence	536	1,002.6
Ponesimod 2/3/4/5/6/7/8/9/10/20 mg repeated sequence	12	21.2
Ponesimod 10 mg	147	240.4
Ponesimod 10/20 mg sequence	134	229.8
Ponesimod 10/20 mg repeated sequence	6	12.7
Ponesimod 10/20/40 mg sequence	141	209.0
Ponesimod 10/20/40 mg repeated sequence	4	5.5
Missing doses in the sequence or any other sequence (partial, reversed, mixed)	20	27.8
Any dose sequence	1,000	1,748.9

[1] Irrespective of study treatment interruptions.
[2] Trials included in the All Randomized (R) Clinical Trials Population are AC-058B201 (24-week double-blind placebo control phase), AC-058B301 (108-week double-blind active control phase), and AC-058B202 treatment period 1 (TP1).
[3] Ponesimod doses received at any time by a subject ie, during up-titration (first dose or at re-initiation) or double-blind phase and/or randomized phases (TP1).
[4] A subject is counted in the dose sequence if (s)he received all doses indicated within the sequence during initial up-titration and maintenance.

All doses received including doses received during re-initiation are considered for the patients-year calculation.

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Table SIII.12: Clinical Trial Exposure[1] to Ponesimod in All Randomized Trials[2] by Race

INDICATION: Multiple Sclerosis		
Race	**Patients**	**Patient-years**
White	968	1,700.3
Black	14	20.9
Asian	2	2.6
Other[3]	16	25.2
All patients	1,000	1,748.9

[1] Irrespective of study treatment interruptions.
[2] Trials included in the All Randomized (R) Clinical Trials Population are AC-058B201 (24-week double-blind placebo control phase), AC-058B301 (108-week double-blind active control phase), and AC-058B202 treatment period 1 (TP1).
[3] Other includes Hispanic, American Indian or Alaska native, Native Hawaiian or Other Pacific Islander, Not applicable, Multiple, Not reported, Other, Unknown.
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Exposure in All Clinical Trials

The All Clinical Trials (CT) Population includes 4 trials:

- Trial B201 (24-week double-blind placebo control phase)
- Trial B202 (treatment periods up to data cutoff date 18 March 2020; investigator and subject blind until the end of TP2[2])
- Trial B301 (108-week double-blind active control phase)
- Trial B303 (open-label treatment phase up to data cutoff date 18 March 2020)

Exposure to ponesimod in the CT population is summarized in Tables SIII.13 through SIII.18 for all subjects by duration, by age group and sex, by dose, by maximum dose, by dose sequence received, and by race.

[2] During TP2, subjects receive 10 or 20 mg ponesimod; during TP3, all subjects receive 20 mg ponesimod.

Table SIII.13: Clinical Trial Exposure[1] to Ponesimod in All Clinical Trials[2] by Duration of Exposure

INDICATION: Multiple Sclerosis		
Duration of exposure[2]	**Patients**	**Patient-years**
≥1 day	1,438	4,975.4
≥3 months	1,336	4,965.3
≥6 months	1,270	4,938.4
≥1 year	1,194	4,874.1
≥2 years	849	4,328.3
≥3 years	704	4,005.5
≥4 years	410	2,973.4
≥5 years	253	2,316.8
≥6 years	241	2,251.7
≥7 years	232	2,191.2
≥8 years	222	2,116.0
≥9 years	192	1,853.0
≥10 years	33	333.8

1 Irrespective of study treatment interruptions, except planned pregnancy interruptions.

2 Trials included in the All Clinical Trials (CT) Population are AC-058B201 (24-week double-blind placebo control phase), AC-058B301 (108-week double-blind active control phase), AC-058B202 treatment periods (up to data cutoff date 18 March 2020; investigator and subject blind until the end of TP2), and AC-058B303 (open-label phase up to data cutoff date: 18 March 2020).

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Table SIII.14: Clinical Trial Exposure[1] to Ponesimod in All Clinical Trials[2] by Age Group and Sex

INDICATION: Multiple Sclerosis						
	Men		**Women**		**All**	
Age group	**Patients**	**Patient-years**	**Patients**	**Patient-years**	**Patients**	**Patient-years**
<18 years	0	0.0	0	0.0	0	0.0
18-30 years	134	529.3	217	757.6	351	1,286.8
31-40 years	191	689.9	356	1,274.6	547	1,964.5
41-55 years	163	512.4	371	1,201.5	534	1,713.9
>55 years	2	3.4	4	6.8	6	10.2
All patients	490	1,735.0	948	3,240.4	1,438	4,975.4

1 Irrespective of study treatment interruptions, except planned pregnancy interruptions.

2 Trials included in the All Clinical Trials (CT) Population are AC-058B201 (24-week double-blind placebo control phase), AC-058B301 (108-week double-blind active control phase), AC-058B202 treatment periods (up to data cutoff date 18 March 2020; investigator and subject blind until the end of TP2), and AC-058B303 (open-label phase up to data cutoff date: 18 March 2020).

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Table SIII.15: Clinical Trial Exposure[1] to Ponesimod in All Clinical Trials[2] by Dose

INDICATION: Multiple Sclerosis		
Dose of exposure[4]	**Patients**	**Patient-years**
Ponesimod 2 mg	1,003	8.2
Ponesimod 3 mg	1,002	8.1
Ponesimod 4 mg	1,001	8.2
Ponesimod 5 mg	1,001	4.1
Ponesimod 6 mg	1,000	4.0
Ponesimod 7 mg	999	4.1
Ponesimod 8 mg	999	4.0
Ponesimod 9 mg	999	4.0
Ponesimod 10 mg	1,433	927.1
Ponesimod 20 mg	1,366	3,778.9
Ponesimod 40 mg	147	224.1
Any ponesimod dose	1,438	4,975.4

[1] Irrespective of study treatment interruptions, except planned pregnancy interruptions.
[2] Trials included in the All Clinical Trials (CT) Population are AC-058B201 (24-week double-blind placebo control phase), AC-058B301 (108-week double-blind active control phase), AC-058B202 treatment periods (up to data cutoff date 18 March 2020; investigator and subject blind until the end of TP2), and AC-058B303 (open-label phase up to data cutoff date: 18 March 2020).
[3] Ponesimod doses received at any time by a subject ie, during up-titration (first dose or at re-initiation) or double-blind randomized phase and/or open-label phases.
[4] Multiple doses per subject are considered. A subject is counted in each of the dose categories if (s)he received at least one dose within that category.

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Table SIII.16: Clinical Trial Exposure[1] to Ponesimod in All Clinical Trials[2] by Maximum Dose[3]

INDICATION: Multiple Sclerosis		
Dose of exposure	**Patients**	**Patient-years**
Ponesimod 2 mg	1	0.0
Ponesimod 3 mg	1	0.0
Ponesimod 4 mg	0	0.0
Ponesimod 5 mg	1	0.0
Ponesimod 6 mg	1	0.0
Ponesimod 7 mg	0	0.0
Ponesimod 8 mg	0	0.0
Ponesimod 9 mg	0	0.0
Ponesimod 10 mg	68	123.6
Ponesimod 20 mg	1,219	3,401.0
Ponesimod 40 mg	147	224.1
Any ponesimod dose	1,438	4,975.4

[1] Irrespective of study treatment interruptions, except planned pregnancy interruptions.
[2] Trials included in the All Clinical Trials (CT) Population are AC-058B201 (24-week double-blind placebo control phase), AC-058B301 (108-week double-blind active control phase), AC-058B202 treatment periods (up to data cutoff date 18 March 2020; investigator and subject blind until the end of TP2), and AC-058B303 (open-label phase up to data cutoff date: 18 March 2020).
[3] Ponesimod maximum dose received at any time by a subject. A subject is counted only in one dose category.

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Table SIII.17: Clinical Trial Exposure[1] to Ponesimod in All Clinical Trials[2] by Dose Sequence Received[3]

INDICATION: Multiple Sclerosis		
Dose of exposure[4]	**Patients**	**Patient-years**
Ponesimod 2/3/4/5/6/7/8/9/10/20 mg sequence	537	768.1
Ponesimod 2/3/4/5/6/7/8/9/10/20 mg repeated sequence	422	1,517.9
Ponesimod 10 mg	65	123.5
Ponesimod 10/20 mg sequence	201	1,468.7
Ponesimod 10/20 mg repeated sequence	20	172.4
Ponesimod 10/20/40 mg sequence	50	29.5
Ponesimod 10/20/40 mg repeated sequence	2	1.2
Ponesimod 10/20/40/10/20 mg sequence[5]	30	286.0
Ponesimod 10/20/40/10/20/10/20 mg sequence	2	19.2
Ponesimod 10/20/40/20 mg sequence[6]	41	346.3
Ponesimod 10/20/40/20/10/20 mg sequence	1	3.7
Missing doses in the sequence or any other sequence (partial, reversed, mixed)	67	239.0
Any dose sequence	1,438	4,975.4

[1] Irrespective of study treatment interruptions, except planned pregnancy interruptions.
[2] Trials included in the All Clinical Trials (CT) Population are AC-058B201 (24-week double-blind placebo control phase), AC-058B301 (108-week double-blind active control phase), AC-058B202 treatment periods (up to data cutoff date 18 March 2020; investigator and subject blind until the end of TP2), and AC-058B303 (open-label phase up to data cutoff date: 18 March 2020).
[3] Ponesimod doses received at any time by a subject ie, during up-titration (first dose or at re-initiation) or double-blind randomized phase and/or open-label phases.
[4] A subject is counted in the dose sequence if (s)he received all doses indicated within the sequence during initial up-titration and maintenance.
[5] Based on the B202 trial design, allowing dose reduction and up-titration in treatment periods TP2 and TP3, respectively.
[6] Based on the B202 trial design, allowing dose reduction and maintenance in treatment periods TP2 and TP3.

All doses received including doses received during re-initiation is considered for the patients-year calculation.
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Table SIII.18: Clinical Trial Exposure[1] to Ponesimod in All Clinical Trials[2] by Race

INDICATION: Multiple Sclerosis		
Race	**Patients**	**Patient-years**
White	1,398	4,859.4
Black	16	59.4
Asian	2	6.3
Other[3]	22	50.4
All patients	1,438	4,975.4

[1] Irrespective of study treatment interruptions, except planned pregnancy interruptions.
[2] Trials included in the All Clinical Trials (CT) Population are AC-058B201 (24-week double-blind placebo control phase), AC-058B301 (108-week double-blind active control phase), AC-058B202 treatment periods (up to data cutoff date 18 March 2020; investigator and subject blind until the end of TP2), and AC-058B303 (open-label phase up to data cutoff date: 18 March 2020).
[3] Other includes Hispanic, American Indian or Alaska native, Native Hawaiian or Other Pacific Islander, Not applicable, Multiple, Not reported, Other, Unknown.

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PART II: SAFETY SPECIFICATION

Module SIV: Populations Not Studied in Clinical Trials

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

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 1	**Pregnant women**
Reason for being an exclusion criterion	Per International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, pregnant women should normally be excluded from clinical trials. Nonclinical safety testing of ponesimod indicates an embryotoxic and teratogenic potential.
Considered to be included as missing information	No
Rationale (if not included as missing information)	Reproductive and embryofetal toxicity is an important potential risk. Ponesimod is contraindicated during pregnancy and in women of childbearing potential not using effective contraception.
Criterion 2	**Lactating women**
Reason for being an exclusion criterion	Lactating women are usually excluded from clinical trials for ethical reasons. There are no data on the presence of ponesimod in human milk or the effects on the breast-fed infant. A study in lactating rats indicated excretion of ponesimod in milk. A risk to newborns/infants cannot be excluded.
Considered to be included as missing information	No
Rationale (if not included as missing information)	The use of ponesimod by breast-feeding women is not anticipated, as the summary of product characteristics (SmPC; Section 4.6) states that ponesimod should not be used during breast-feeding.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program	
Criterion 3	**Subjects with active systemic bacterial, viral, or fungal infections (including positive hepatitis B surface antigen or hepatitis C antibody test), subjects with active or latent tuberculosis, subjects with severe immunodeficiency (including positive human immunodeficiency virus test), subjects with negative antibody test for varicella zoster virus (VZV) infection, or subjects with known PML infection (including magnetic resonance imaging [MRI] signs compatible with a diagnosis of PML infection)**
Reason for being an exclusion criterion	Ponesimod reduces the number of circulating lymphocytes. This pharmacological effect might increase the risk of infections as a consequence of reduced immunosurveillance. Inclusion of subjects with severe infections or immunocompromised subjects could confound the safety evaluation.
Considered to be included as missing information	No
Rationale (if not included as missing information)	Serious opportunistic infections including PML is an important potential risk. Ponesimod is contraindicated in patients with severe active infections, in patients with active chronic infections, and in patients in an immunodeficient state.
Criterion 4	**History or presence of malignancy (except for surgically excised basal or squamous cell skin lesions), or lymphoproliferative disease** **Presence of precancerous (eg, actinic keratosis, atypical moles) or cancerous skin lesions (eg, basal cell carcinoma, squamous cell carcinoma)**
Reason for being an exclusion criterion	Ponesimod reduces the number of circulating lymphocytes. This pharmacological effect might increase the risk of malignancy as a consequence of reduced immunosurveillance. An increased risk of cutaneous malignancies has also been reported in association with another S1P receptor modulator. Inclusion of subjects with history or presence of malignancy or lymphoproliferative disease or presence of precancerous or cancerous skin lesions could confound the safety evaluation.
Considered to be included as missing information	No
Rationale (if not included as missing information)	Skin cancer and non-skin malignancy are important potential risks. Ponesimod is contraindicated in patients with active malignancies.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program	
Criterion 5	**Presence of macular edema**
Reason for being an exclusion criterion	Macular edema is a known class effect of S1P receptor modulators. Inclusion of subjects with macular edema could confound the safety evaluation.
Considered to be included as missing information	No
Rationale (if not included as missing information)	Macular edema is an important identified risk.
Criterion 6	**Any of the following cardiovascular conditions:** - **Resting HR <50 beats per minute (bpm) as measured by 12-lead electrocardiogram (ECG)** - **Myocardial infarction within the last 6 months or ongoing unstable ischemic heart disease** - **Cardiac failure (New York Heart Association class III or IV) or any severe cardiac disease** - **History or presence of valvular heart disease associated with symptoms or significant hemodynamic change according to investigator judgment** - **History or presence of cardiac rhythm disorders (eg, sino-atrial heart block, symptomatic bradycardia, atrial flutter or atrial fibrillation, ventricular arrhythmias, cardiac arrest)** - **Presence of second-degree AV block Mobitz type II or third-degree AV block, or a QT corrected for heart rate based on Fridericia's formula (QTcF) interval >470 ms (women), >450 ms (men) as measured by 12-lead ECG** - **History of syncope associated with cardiac disorders** - **Systemic arterial hypertension not controlled by medication according to the investigator's judgment**
Reason for being an exclusion criterion	Data from nonclinical studies and Phase 1 clinical trials indicated transient HR and AV conduction effects following ponesimod administration. Bradyarrhythmia is a known class effect of S1P receptor modulators.
Considered to be included as missing information	No
Rationale (if not included as missing information)	Bradyarrhythmia occurring post-first dose is an important identified risk. Ponesimod is contraindicated in patients who have experienced myocardial infarction, unstable angina, stroke, transient ischemic attack (TIA), decompensated heart failure requiring hospitalization, or New

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program	
	York Heart Association (NYHA) Class III or IV heart failure in the last 6 months and in patients who have presence of Mobitz type II second-degree AV block, third-degree AV block, or sick-sinus syndrome, unless the patient has a functioning pacemaker. In addition, the SmPC (Section 4.4) states that advice from a cardiologist should be obtained before initiation of ponesimod to determine overall benefit-risk and the most appropriate monitoring strategy • in patients with significant QT prolongation (QT corrected [QTc] >500 ms) or who are already being treated with QT-prolonging medicinal products with known arrhythmogenic properties (risk of torsades de pointes); • in patients with atrial flutter/fibrillation or arrhythmias treated with Class Ia (eg, quinidine, procainamide) or Class III (eg, amiodarone, sotalol) anti-arrhythmic medicinal products; • in patients with unstable ischemic heart disease, cardiac decompensated failure occurring more than 6 months prior to treatment initiation, history of cardiac arrest, cerebrovascular disease (TIA, stroke occurring more than 6 months prior to treatment initiation), and uncontrolled hypertension, since significant bradycardia may be poorly tolerated in these patients; • in patients with a history of Mobitz Type II second-degree AV block or higher-grade AV block, sick-sinus syndrome, or sino-atrial heart block; • in patients with a history of recurrent syncope or symptomatic bradycardia; • in patients receiving concurrent therapy with drugs that decrease HR (eg, beta-blockers, nondihydropyridine calcium channel blockers [diltiazem and verapamil], other drugs that may decrease HR, such as digoxin).

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program	
Criterion 7	**Type 1 or 2 diabetes that is poorly controlled according to the investigator's judgment, or diabetes complicated with organ involvement such as nephropathy or retinopathy**
Reason for being an exclusion criterion	Inclusion of subjects with these conditions could confound the safety and efficacy evaluations. In addition, there is an increased risk of macular edema in patients with diabetic retinopathy and an increased prevalence of cardiovascular comorbidities in this patient population.
Considered to be included as missing information	No
Rationale (if not included as missing information)	This exclusion criterion was implemented for the purpose of the clinical trials and not for a specific safety concern. Macular edema, which is a complication of diabetic retinopathy, is an important identified risk.
Criterion 8	**Subjects with a clinically significant pulmonary condition including:** - **Asthma that is insufficiently controlled according to the investigator's judgment, or any hospitalization due to asthma exacerbation within the last 6 months** - **Abnormal pulmonary function tests (PFTs): forced expiratory volume in 1 second (FEV_1) or forced vital capacity (FVC) <70% of the predicted normal value**
Reason for being an exclusion criterion	Data from nonclinical studies and Phase 1 clinical trials indicated effects of ponesimod on pulmonary function. Dose-dependent reductions in FEV_1 and FVC are known class effects of S1P receptor modulators. Inclusion of subjects with clinically significant pulmonary conditions could confound the safety evaluation.
Considered to be included as missing information	No
Rationale (if not included as missing information)	Bronchoconstriction is an important identified risk.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program	
Criterion 9	**Lymphocyte count <0.8×10^9/L (<800/mm^3)**
Reason for being an exclusion criterion	Inclusion of subjects with these types of abnormal laboratory values could confound the safety evaluation. Based on its mechanism of action, ponesimod may lead to additive immune system effects in subjects with an abnormal blood count.
Considered to be included as missing information	No
Rationale (if not included as missing information)	This exclusion criterion was implemented in the clinical trials to reduce potential confounding of the assessment of safety.
Criterion 10	**Subjects with a hepatic condition including:** - **Known history of active hepatitis B or C any time prior to randomization or known history of active hepatitis A within the last 3 years** - **Presence of chronic liver or biliary disease** - **Moderate or severe hepatic impairment defined as Child Pugh class B or C, respectively, based on measurement of total bilirubin, serum albumin, international normalized ratio (INR), as well as on presence/absence and severity of ascites and hepatic encephalopathy** - **Any of the following abnormal laboratory values: alanine aminotransferase [ALT] >2 x the upper limit of normal (ULN), aspartate aminotransferase [AST] >2xULN, or total bilirubin >1.5xULN (unless in the context of known Gilbert's syndrome)**
Reason for being an exclusion criterion	Ponesimod is metabolized in the liver. Results of a Phase 1 trial in subjects with hepatic impairment (AC-058-112) showed clinically relevant effects on the PK of ponesimod (single dose of 10 mg ponesimod) in subjects with moderate or severe hepatic impairment. Patients with pre-existing liver conditions may be susceptible to liver injury.
Considered to be included as missing information	No
Rationale (if not included as missing information)	Severe liver injury is an important potential risk. Ponesimod is contraindicated in patients with moderate or severe hepatic impairment (Child Pugh class B and C, respectively). In addition, the SmPC (Section 4.4) states that caution should be exercised when using ponesimod in patients with a history of significant liver disease. Patients who develop symptoms suggestive of hepatic dysfunction should be monitored for hepatotoxicity, and ponesimod should be discontinued if significant liver injury is confirmed.

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

The clinical development program is unlikely to detect rare adverse reactions such as PML and cryptococcal infections, rare adverse reactions with a long latency, or adverse reactions caused by prolonged or cumulative exposure such as malignancies.

SIV.3. Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Program(s)

Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	Although prohibited by protocol, exposure to ponesimod during pregnancy occurred in the clinical development program. Through the data lock point of this RMP, 15 cases of fetal exposure (ie, onset of pregnancy occurring during study drug administration or within 30 days after study drug discontinuation) to ponesimod were reported across completed and ongoing clinical trials.
Breast-feeding women	Breast-feeding women were not included in the clinical development program.
Population with relevant different ethnic origin	Of the 1,438 subjects treated with ponesimod in the CT population, 1,398 (97.2%) were white, 16 (1.1%) were black, 2 (<1%) were Asian, and 22 (1.5%) were of another race/ethnic origin (ie, Hispanic, American Indian or Alaska native, Native Hawaiian or Other Pacific Islander, Not applicable, Multiple, Not reported, Other, or Unknown).
Subpopulations carrying relevant genetic polymorphisms	Not applicable.
Pediatric patients	Subjects <18 years of age were not included in the clinical development program.
Elderly patients	Subjects ≥65 years of age were not included in the clinical development program.
Patients with relevant comorbidities:	
Patients with hepatic impairment	Subjects with moderate or severe hepatic impairment (Child Pugh class B or C) were not included in the Phase 2b and Phase 3 clinical trials.
Patients with renal impairment	Subjects with severe renal function impairment (Cockroft-Gault estimated creatinine clearance <30 mL/min) were not included in the Phase 2b and Phase 3 clinical trials.
Patients with cardiovascular comorbidities	Subjects with cardiovascular conditions were not included in the clinical development program.

Type of Special Population	Exposure
Immunocompromised patients	Subjects with severe infections were not included in the clinical development program.
Patients with a disease severity different from inclusion criteria in clinical trials	Not applicable.

Summary of Missing Information Due to Limitations of the Clinical Trial Program

Use in elderly patients
Long-term safety of ponesimod

PART II: SAFETY SPECIFICATION

Module SV: Postauthorization Experience

SV.1. Postauthorization Exposure

SV.1.1. Method used to Calculate Exposure

Reporting frequencies calculated using exposure data do not reflect occurrence rates. Multiple factors influence the reporting of spontaneous experiences and therefore, caution must be exercised in the analysis and evaluation of spontaneous reports. In addition, product exposure is estimated at the time of distribution, not at the time of usage. There is a delay between the time medication is distributed until it is used by a patient.

Patient exposure was estimated by calculation from distribution data. Estimates of exposure are based upon finished product. Based on the Company Core Data Sheet, the recommended dose for ponesimod includes a starter pack that must be used for the patients initiating treatment with ponesimod. The patients initiate ponesimod treatment with a 14 day titration, starting with a 2 mg tablet orally once daily, and progress with the titration schedule. After titration is complete, the recommended maintenance dosage of ponesimod is a 20 mg tablet taken orally once daily. Assuming that all patients are compliant with their treatment, the average total dose is 501.5 mg per month (ie, equal to 1 person month).

SV.1.2. Exposure

The cumulative exposure to ponesimod by region is presented below in Table SV.1.

Table SV.1: Exposure to Ponesimod (Launch to 31 March 2023)

Region	Total Milligrams	Person-Months	Person-Years
EU	12,899,378	25,722	2,143
NA	6,370,922	12,703	1,059
ROW	1,515,267	3,021	252
Worldwide Total[a]	**20,785,567**	**41,446**	**3,454**

Key: EU=European Union; NA=North America; ROW=Rest of World

[a.] The distribution was first observed in April 2021.

Based on the 20,785,567 mg distributed worldwide by the Company from launch to 31 March 2023, the estimated exposure to ponesimod is 41,446 person-months or 3,454 person-years.

PART II: SAFETY SPECIFICATION

Module SVI: Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

Ponesimod has not been shown to have any abuse liability. Therefore, there is no concern for misuse for illegal purposes.

PART II: SAFETY SPECIFICATION

Module SVII: Identified and Potential Risks

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

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

Reason for not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP:

Note: Medical Dictionary for Regulatory Activities (MedDRA) terms (System Organ Classes [SOCs] and preferred terms [PTs]) are used to group the risks not considered important for inclusion in the list of safety concerns.

Risks not Included in the List of Safety Concerns in the RMP
Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):
Infections and infestations: nasopharyngitis, upper respiratory tract infection, urinary tract infection, bronchitis, influenza, rhinitis, respiratory tract infection, respiratory tract infection viral, pharyngitis, sinusitis, viral infection, laryngitis, pneumonia
Psychiatric disorders: depression, insomnia, anxiety
Nervous system disorders: dizziness, hypoesthesia, somnolence, migraine
Ear and labyrinth disorders: vertigo
Gastrointestinal disorders: dyspepsia, dry mouth
Musculoskeletal and connective tissue disorders: back pain, arthralgia, pain in extremity, ligament sprain, joint swelling
General disorders and administration site conditions: fatigue, pyrexia, edema peripheral, chest discomfort
Investigations: ALT increased, AST increased, hypercholesterolemia, hepatic enzyme increased, C-reactive protein increased, transaminases increased, blood cholesterol increased, hyperkalemia
Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:
Not applicable

Risks not Included in the List of Safety Concerns in the RMP
Known risks that require no further characterization and are followed up via routine pharmacovigilance and for which the risk minimization messages in the product information are adhered by prescribers (eg, actions being part of standard clinical practice in each EU Member state where the product is authorized):
Vascular disorders: hypertension
Known risks that do not impact the risk-benefit profile:
Not applicable
Other reasons for considering the risks not important:
Blood and lymphatic system disorders: lymphopenia, lymphocyte count decreased. These events are attributed to the mechanism of action of ponesimod. The potential clinical consequences are adequately covered under the important potential risk of Serious opportunistic infections including PML.

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

Safety Concerns for Inclusion in the RMP	Risk-benefit Impact
Important identified risks	
Bradyarrhythmia occurring post-first dose	In guinea pigs, single doses of ponesimod ≥0.3 mg/kg/day induced AV blocks and decreased HR. These cardiovascular effects were significantly reduced on repeat dosing and after a low starting dose and up-titration (desensitization). Transient HR reductions and, less frequently, transient first- or second-degree AV blocks have been observed in the first days of treatment with ponesimod during the clinical development program. Bradyarrhythmia occurring post-first dose is substantially mitigated through gradual up-titration of ponesimod. The SmPC and package leaflet (PL), as well as the educational materials for healthcare professionals (HCPs) and patients/caregivers, provide information on how to manage the risk. Overall, the risk-benefit balance for the product is positive considering the severity of the disease treated and the potential efficacy for patients treated with ponesimod.

Safety Concerns for Inclusion in the RMP	Risk-benefit Impact
Macular edema	Although macular edema occurred in subjects who received ponesimod in the clinical development program, the observed incidence was low and the events resolved after study treatment discontinuation. The SmPC and PL, as well as the educational materials for HCPs and patients/caregivers, provide information on how to manage the risk. Overall, the risk-benefit balance for the product is positive considering the severity of the disease treated and the potential efficacy for patients treated with ponesimod.
Bronchoconstriction	Most adverse events (AEs) suggestive of bronchoconstriction were mild or moderate in severity, and dose-dependent reductions in FEV_1 and reductions in diffusing capacity of the lungs for carbon monoxide (DL_{CO}) appeared to be partially reversible after study treatment discontinuation. The SmPC and PL, as well as the educational materials for HCPs and patients/caregivers, provide information on how to manage the risk. Overall, the risk-benefit balance for the product is positive considering the severity of the disease treated and the potential efficacy for patients treated with ponesimod.
Important potential risks	
Severe liver injury	Most treatment-emergent adverse events (TEAEs) suggestive of liver injury were mild or moderate in severity and resolved during ponesimod treatment or after treatment discontinuation. Severe and serious events were confounded by concurrent medical conditions. The SmPC and PL, as well as the educational materials for HCPs and patients/caregivers, provide information on how to manage the risk. Overall, the risk-benefit balance for the product is positive considering the severity of the disease treated and the potential efficacy for patients treated with ponesimod.
Serious opportunistic infections including PML	Because of its mechanism of action, ponesimod may increase the risk of serious opportunistic infections including PML. The majority of the reported TEAEs suggestive of serious opportunistic infections (VZV reactivation and candidiasis) were mild or moderate in severity, occurred as single events, and resolved during ponesimod treatment. No cases of fatal or life-threatening infections such as cryptococcal meningitis (CM) or PML have been reported in ponesimod-treated subjects. The SmPC and PL, as well as the educational materials for HCPs and patients/caregivers, provide information on how to manage the risk. Overall, the risk-benefit balance for the product is positive considering the severity of the disease treated and the potential efficacy for patients treated with ponesimod.

Safety Concerns for Inclusion in the RMP	Risk-benefit Impact
Skin cancer	Because of its mechanism of action, ponesimod may increase the risk of skin cancer. An increased risk of cutaneous malignancies has been reported in association with another S1P receptor modulator. Although skin cancer occurred in subjects treated with ponesimod in the clinical development program, the observed incidence was low. Most cases were mild or moderate in severity and were managed with appropriate treatment. The SmPC and PL, as well as the educational materials for HCPs and patients/caregivers provide information on how to manage the risk. Overall, the risk-benefit balance for the product is positive considering the severity of the disease treated and the potential efficacy for patients treated with ponesimod.
Non-skin malignancy	Because of its mechanism of action, ponesimod may increase the risk of non-skin malignancies. The observed incidence of non-skin malignancies was low in the clinical development program and was similar in subjects treated with ponesimod and subjects treated with placebo or comparator. The nature and types of the observed non-skin malignancies (eg, breast cancer and cervical carcinoma) were in line with those expected in the target population. Overall, the risk-benefit balance for the product is positive considering the severity of the disease treated and the potential efficacy for patients treated with ponesimod.
Reproductive and embryofetal toxicity	Nonclinical data for ponesimod, as well as human experience in patients receiving another S1P receptor modulator, have demonstrated teratogenic effects in offspring. The SmPC and PL, as well as the educational materials for HCPs and patients/caregivers, provide information on how to minimize the risk of reproductive and embryofetal toxicity. Overall, the risk-benefit balance for the product is positive considering the severity of the disease treated and the potential efficacy for patients treated with ponesimod.
Convulsions	Although convulsions occurred in subjects who received ponesimod in the clinical development program, the observed incidence was low. Most cases were mild or moderate in severity, and some cases occurred in subjects with ongoing nervous system conditions at baseline. As convulsions occur at a higher incidence in the MS population, the contribution of ponesimod to these events is unknown. The PL and the educational materials for HCPs and patients/caregivers provide information on how to manage the risk. Overall, the risk-benefit balance for the product is positive considering the severity of the disease treated and the potential efficacy for patients treated with ponesimod.
Unexpected neurological or psychiatric symptoms/signs (PRES, ADEM, atypical MS relapses)	Although rare cases of posterior reversible encephalopathy syndrome (PRES) and acute disseminated encephalomyelitis (ADEM)-like events have been reported in patients receiving an S1P receptor modulator, such events have not been reported in ponesimod clinical trials. The SmPC and PL, as well as the educational materials for HCPs and patients/caregivers, provide information on how to manage the risk. Overall, the risk-benefit balance for the product is positive considering the severity of the disease treated and the potential efficacy for patients treated with ponesimod.
Missing information	

Safety Concerns for Inclusion in the RMP	Risk-benefit Impact
Use in elderly patients	Clinical trials of ponesimod did not include patients aged 65 years and older. The results from a population PK analysis indicated that age (range: 17-65 years) does not significantly influence the PK of ponesimod. However, ponesimod should be prescribed with caution in patients aged 65 years and older due to the lack of data on safety and efficacy.
Long-term safety of ponesimod	Although safety data are available for subjects treated with ponesimod for ≥10 years in clinical trials, there is a limited number of subjects with long-term exposure to ponesimod. Of the 1,438 subjects treated with ponesimod in the CT population, 849 subjects were exposed ≥2 years, 253 were exposed ≥5 years, 222 were exposed ≥8 years, 192 subjects were exposed ≥9 years, and 33 subjects were exposed ≥10 years. Long-term extension trials (B202 and B303) are ongoing to further characterize the long-term safety profile of ponesimod.

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

Not applicable.

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

Important identified risks

1. Bradyarrhythmia occurring post-first dose
2. Macular edema
3. Bronchoconstriction
4. Convulsions

Important potential risks

1. Severe liver injury
2. Serious opportunistic infections including PML
3. Skin cancer
4. Non-skin malignancy
5. Reproductive and embryofetal toxicity
6. Unexpected neurological or psychiatric symptoms/signs (PRES, ADEM, atypical MS relapses)

Missing information:

1. Use in elderly patients
2. Long-term safety of ponesimod

MedDRA version 21.0 was used to classify the clinical trials AE information that is summarized in this section.

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

Important Identified Risk: Bradyarrhythmia occurring post-first dose

Potential Mechanisms:

Activation of S1P receptors leads to transient bradycardia in both animals and humans. In atrial myocytes, stimulation of S1P receptors by S1P leads to activation of the G-protein-coupled inwardly rectifying potassium (GIRK, also known as Kir3) channels. This effect is linked to S1P receptor-dependent activation of GIRK channels on atrial myocytes and results in hyperpolarization and a temporary reduction in excitability (Camm 2014).

Evidence Source(s) and Strength of Evidence:

In guinea pigs, single doses of ponesimod ≥0.3 mg/kg/day induced AV blocks and decreased HR. These cardiovascular effects were significantly reduced on repeat dosing and after a low starting dose and up-titration (desensitization).

Transient HR reductions and, less frequently, transient first- or second-degree AV blocks have been observed in the first days of treatment with ponesimod during the clinical development program. Bradycardia was identified as an adverse reaction. These findings and this adverse reaction are described in the SmPC.

Characterization of the Risk:

Activation of $S1P_1$ receptors during initiation of treatment with ponesimod leads to dose-dependent transient HR decrease and infrequently, AV conduction delays. In the presence of ponesimod, this initial receptor activation is followed by desensitization of the $S1P_1$ system in cardiomyocytes, leading to normalization 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).

Two up-titration regimens were employed in the clinical development program to mitigate the first-dose effects of ponesimod: an up-titration regimen with an initial ponesimod dose of 10 mg in Phase 2 trials (B201 and B202) and a gradual up-titration regimen starting with a ponesimod dose of 2 mg in Phase 3 trials (B301 and B303).

The up-titration regimen with ponesimod starting with 10 mg for 7 days, followed by 20 mg for 7 days, then followed by 40 mg was initially investigated in Phase 1 trials and was subsequently used in the Phase 2 trials in subjects with MS (Trials B201 and B202; a starting dose of 10 mg once daily in all ponesimod groups was followed by an up-titration [or mock up-titration] to 20 mg and 40 mg starting on Days 8 and 15, respectively). Although this up-titration regimen mitigated first-dose effects on HR and AV conduction, events of bradycardia and second-degree AV blocks

were still reported in a small proportion of subjects. Further investigations using PK/PD modeling and simulation of the HR effects were performed and a new gradual up-titration regimen was developed (2 mg, 2 mg, 3 mg, 3 mg, 4 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 10 mg, and 10 mg once daily [ie, over 14 days]). In the Phase 1 Trial AC-058-115, ponesimod was titrated from 2 to 20 mg in 10 steps over 14 days. Based on extensive 12-lead ECG and Holter monitoring, the study results showed that this new gradual up-titration regimen starting at a dose of ponesimod 2 mg can successfully mitigate the occurrence of a clinically relevant first-dose cardiodynamic effect in healthy subjects (Juif 2017).

The up-titration regimen starting at ponesimod 2 mg and gradually reaching the therapeutic maintenance dose of 20 mg over 15 days was implemented in the Phase 3 clinical program. To further mitigate the risk of symptomatic bradycardia or AV blocks, specific safety measures were implemented in the B301 study protocol. Subjects with resting HR <50 bpm or those with relevant cardiac comorbidities were excluded from the trial. Concomitant treatment with digoxin, beta-blockers, diltiazem, verapamil, or any other HR-lowering drugs were not permitted. During treatment initiation, cardiac monitoring was performed using 12-lead ECGs and blood pressure measurements on an hourly basis for at least 4 hours post-first dose. Discharge criteria following the first-dose cardiac monitoring (HR >45 bpm, and if HR <50 bpm, it must not be the lowest value post dose, systolic blood pressure >90 mmHg, and no persisting significant ECG abnormality) and discontinuation criteria were defined in the study protocol and required that subjects discontinue the study drug in cases of clinically relevant bradycardia or other specific ECG findings.

In Trial B301, 565 subjects with RMS were exposed to ponesimod initiation treatment using the gradual up-titration regimen starting at ponesimod 2 mg (compared with 566 subjects exposed to teriflunomide 14 mg initiating treatment with a mock up-titration in order to maintain the study blind). On Day 1, a higher proportion of subjects (2.1%) in the ponesimod 20-mg group had at least 1 treatment-emergent HR and rhythm adverse event of special interest (AESI; including hypotension; refer to Annex 7.3 for the list of MedDRA terms) compared to 0.4% in the teriflunomide 14-mg group. No cases of second-degree or third-degree AV block, presyncope, or syncope were reported on Day 1. None of the events was serious or led to discontinuation. In the ponesimod 20-mg group, the most frequently reported HR and rhythm AESIs on Day 1 were bradycardia (0.7%) and first-degree AV block (0.5%). From Day 2 to Day 16, a total of 4 subjects reported HR and rhythm AESIs in the ponesimod 20-mg group; none was serious or led to discontinuation. From Day 17 onwards, no HR and rhythm AESIs of concern and no second-degree AV block were reported in the ponesimod 20-mg group.

In the subset of subjects with at least 1 re-initiation using the up-titration regimen (n=19 on ponesimod 20 mg, n=16 on teriflunomide 14 mg), no HR and rhythm AESIs (including hypotension) occurred on Day 1 to Day 16 in the ponesimod 20-mg group following re-initiation of study treatment.

Maximum mean reduction in HR from pre- to postdose on Day 1 was observed at 2 hours postdose in the ponesimod 20-mg group (-8.7 bpm) compared to -1.7 bpm in the teriflunomide 14-mg group.

On Day 1, 3 (0.5%) subjects in the ponesimod 20-mg group had an asymptomatic postdose HR ≤40 bpm compared to no subjects on teriflunomide 14 mg; all 3 subjects had an HR <55 bpm at their baseline visit.

There were 2.7% of subjects in the ponesimod 20-mg group and 0.4% in the teriflunomide 14-mg group who had a PR prolongation to >200 ms, with an increase from predose of >20 ms, on Day 1. A total of 0.7% and 0.4% of subjects in the ponesimod 20-mg and teriflunomide 14-mg groups, respectively, had QTcF prolongation to >450 ms, with an increase from predose of >30 ms, on Day 1. No subjects had treatment-emergent QTcF interval >480 ms.

New ECG findings at any postdose assessment on Day 1 or Day 1 following re-initiation of study drug were observed in 17.5% of subjects in the ponesimod 20-mg group versus 12.2% of subjects in the teriflunomide 14-mg group. Sinus bradycardia was reported in 5.8% of subjects in the ponesimod 20-mg group versus 1.6% in the teriflunomide 14-mg group, and first-degree AV block was reported in 3.4% of subjects in the ponesimod 20-mg group versus 1.2% in the teriflunomide 14-mg group.

In the subset of subjects with at least 1 re-initiation, no subjects had postdose PR or QTc prolongation or an HR ≤40 bpm on Day 1 following re-initiation of study drug.

Additionally, up to a data cutoff date of 30 May 2019, 877 subjects were exposed to ponesimod in the long-term extension Phase 3 Trial B303, with 438 subjects newly exposed to ponesimod following previous teriflunomide 14-mg treatment in Trial B301. On Day 1 of Trial B303, 0.7% of subjects had at least 1 HR and rhythm AESI (including hypotension). None of these events was serious or led to discontinuation. From Day 2 to Day 16, 1 subject had an AE of first-degree AV block. From Day 17 onwards, no HR and rhythm AESIs of concern, including no second-degree AV block, were reported.

In the subset of subjects with at least 1 re-initiation in extension Trial B303, no TEAEs were reported on Day 1 following re-initiation of study drug.

Maximum mean reduction in HR from pre- to postdose on Extension Day 1 was observed at 2 hours postdose, ie, -4.0 bpm (from 69.5 to 65.4 bpm) in the P20 mg/P20 mg group (ie, ponesimod 20 mg in Trial B301/ponesimod 20 mg in Trial B303) and -5.1 bpm (from 69.3 to 64.2 bpm) in the T14 mg/P20 mg group (ie, teriflunomide 14 mg in Trial B301/ponesimod 20 mg in Trial B303).

On Day 1 of extension Trial B303, no subjects had a postdose HR ≤40 bpm and 1.7% of subjects had a PR prolongation to >200 ms, with an increase from predose of >20 ms. A total of 0.8% of subjects (1.2% in P20 mg/P20 mg, 0.5% in T14 mg/P20 mg) had QTcF prolongation to >450 ms, with an increase from predose of >30 ms on Day 1.

New ECG findings (ie, findings not present at any assessment prior to first treatment in the extension trial) at any postdose assessment on Day 1 were reported in 15.2% of subjects (16.0% in P20 mg/P20 mg, 14.4% in T14 mg/P20 mg). These included sinus bradycardia (4.0% overall;

4.1% in P20 mg/P20 mg, 3.9% in T14 mg/P20 mg) and first-degree AV block (2.1% overall; 1.6% in P20 mg/P20 mg, 2.5% in T14 mg/P20 mg). No second-degree AV block was reported.

In the subset of subjects with at least 1 re-initiation (n=6 in P20 mg/P20 mg, n=9 in T14 mg/P20 mg), no subjects had a postdose PR or QTc prolongation or an HR ≤40 bpm on Day 1 following re-initiation of study drug in extension Trial B303. Two subjects in the T14 mg/P20 mg group had new ECG findings (ie, findings not present at any assessment prior to first treatment in the extension trial), including first-degree AV block in 1 subject.

During the interval between the data cutoff dates of 30 May 2019 and 18 March 2020, 6 subjects (2 subjects in the P20 mg/P20 mg group and 4 subjects in the T14 mg/P20 mg group) in the Phase 3 Trial B303 re-initiated ponesimod treatment following a dose interruption of ≥4 days. There were no new HR outliers reported on Day 1 of any re-initiation. The minimum HR value (HR ≤50 bpm) was reported for 1 subject on Day 1 of re-initiation. There were no further reports of second-degree AV block (or higher). No serious AEs or AEs leading to premature discontinuation of study treatment were reported on Day 1 of any re-initiation of ponesimod treatment.

Further analysis of first-dose data from the pivotal Phase 3 trial (B301) was conducted to support the first-dose monitoring only in patients with risk factors for symptomatic bradycardia. In Trial B301, the ECG-related findings on Day 1 were analyzed based on the risk status for symptomatic bradyarrhythmia at baseline (yes or no). The following risk factors were predefined: sinus bradycardia (HR <55 bpm), first- or second-degree (Mobitz type I) AV block present at any ECG prior to initiation of treatment, or cardiac disorders in medical history (reported by any PT of Cardiac disorder SOC). There were more subjects not at risk for symptomatic bradyarrhythmia (n=469 in the ponesimod 20-mg group) than subjects at risk (n=95) at baseline.

In the subset of ponesimod 20-mg-treated subjects at risk for symptomatic bradyarrhythmia at baseline, the incidence of TEAEs in the Cardiac disorders SOC on Day 1 was 3.2% (3 subjects), compared to 1.9% (9 subjects) in the subset of subjects not at risk for symptomatic bradyarrhythmia. None of the TEAEs reported on Day 1 was serious.

In the subset of ponesimod 20-mg-treated subjects at risk for symptomatic bradyarrhythmia, 3 subjects (3.2%) had post-first-dose HR ≤40 bpm on Day 1 compared to none in the subset of subjects not at risk for symptomatic bradyarrhythmia.

On Day 1, in the subset of subjects at risk for symptomatic bradyarrhythmia, the proportion of subjects with a new ECG finding of sinus bradycardia (defined as HR <50 bpm) was 20.0%, compared to 3.0% (all asymptomatic) in the subset of subjects not at risk for symptomatic bradyarrhythmia.

Overall, the risk of first dose effects appeared to be higher in the subset of subjects at risk for symptomatic bradyarrhythmia.

In drug-drug interaction Trial AC-058-111, the effects on HR, blood pressure, and PK interactions of ponesimod with a concomitant calcium channel blocker (diltiazem) or a concomitant beta-

blocker (atenolol) were investigated in healthy subjects. Concomitant administration of atenolol (50 mg) or diltiazem (240 mg) with a single dose of 10 mg ponesimod (without up-titration) suggested an additive PD effect on HR and AV conduction. Bradycardia and AV blocks were observed in both atenolol and diltiazem arms of this trial, including one life-threatening collapse with 1-minute and 20-seconds asystole, which occurred after administration of concomitant treatment of 50 mg atenolol and 10 mg of ponesimod as a single dose without titration. This trial 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 trial.

In the drug-drug interaction trial AC-058-117, effects on HR, blood pressure, and PK interactions of the up-titration regimen of ponesimod were investigated in healthy adult subjects receiving propranolol (a beta-blocker) at steady state. Overall, concomitant administration of ponesimod with beta-blocker propranolol resulted in an additive effect on HR measured by Holter, with the largest mean maximum difference (-12.4 bpm) in mean hourly HR between treatments with and without propranolol observed on the first day of ponesimod treatment (up-titration), and the difference decreased with subsequent doses. No second-degree or higher AV block, or clinically significant sinus pause (>3 seconds) was observed. In all subjects, the mean hourly HR as assessed by Holter was >40 bpm.

Although there is limited experience with concomitant use of beta-blockers in MS trials, ponesimod did not appear to increase the risk for cardiovascular events.

When a gradual up-titration regimen is utilized, bradyarrhythmia occurring at initiation of ponesimod treatment is present in the form of a transient decrease in HR. Rarely, patients may experience AV blocks. The majority of patients with bradyarrhythmia at initiation of ponesimod treatment at 2 mg are asymptomatic; some patients may experience various symptoms which resolve spontaneously.

Risk Factors and Risk Groups:

Risk factors include cardiac rhythm disorders or ECG abnormalities indicative of an increased risk for arrhythmia, low resting HR, history of fainting or collapse, significant QT prolongation (ie, QTc >500 ms), and concurrent therapy with anti-arrhythmic medicinal products, QT prolonging medicinal products, or medicinal products that slow HR.

Patients with pre-existing cardiovascular comorbidities (such as ischemic heart disease, cardiac failure and history of cardiac arrest or myocardial infarction, cerebrovascular disease, uncontrolled hypertension, and presence of AV block) are also at increased risk.

Preventability:

Prior to treatment initiation with ponesimod, an ECG should be obtained in all patients to determine whether pre-existing conduction abnormalities are present.

To reduce the risk of bradyarrhythmia occurring post-first dose, a 14-day up-titration scheme is employed in all patients at treatment initiation and at treatment re-initiation if 4 or more consecutive doses are missed.

First-dose cardiac monitoring is recommended in patients with sinus bradycardia (HR <55 bpm), first- or second-degree (Mobitz type I) AV block, or a history of myocardial infarction or heart failure with onset >6 months prior to treatment initiation and in stable condition. In these patients, the first dose of ponesimod should be administered in a setting where resources to appropriately manage symptomatic bradycardia are available. These patients should be monitored for 4 hours after the first dose for signs and symptoms of bradycardia with a minimum of hourly pulse and blood pressure measurement. An ECG should be obtained in these patients at the end of the 4-hour observation period.

Monitoring should be continued in patients in whom the following abnormalities are present after 4 hours (even in the absence of symptoms) until the abnormality resolves:

- The HR 4 hours postdose is <45 bpm.
- The HR 4 hours postdose is at the lowest value postdose, suggesting that the maximum PD effect on the heart may not have occurred.
- The ECG 4 hours postdose shows new onset second-degree or higher AV block.

If postdose symptomatic bradycardia, bradyarrhythmia, or conduction-related symptoms occur, or if ECG 4 hours postdose shows new onset second-degree or higher AV block or QTc ≥500 ms, appropriate management should be initiated, continuous ECG monitoring should be started, and monitoring should be continued until the symptoms have resolved if no pharmacological treatment is required. If pharmacological treatment is required, monitoring should be continued overnight and 4-hour monitoring should be repeated after the second dose.

Advice from a cardiologist should be obtained before initiation of ponesimod in the following patients to determine overall benefit-risk and the most appropriate monitoring strategy:

- Patients with significant QT prolongation (QTc >500 ms) or who are already being treated with QT-prolonging medicinal products with known arrhythmogenic properties (risk of torsades de pointes).
- Patients with atrial flutter/fibrillation or arrhythmias treated with Class Ia (eg, quinidine, procainamide) or Class III (eg, amiodarone, sotalol) anti-arrhythmic medicinal products.
- Patients with unstable ischemic heart disease, cardiac decompensated failure occurring more than 6 months prior to treatment initiation, history of cardiac arrest, cerebrovascular disease (TIA, stroke occurring more than 6 months prior to treatment initiation), and uncontrolled hypertension, since significant bradycardia may be poorly tolerated in these patients, treatment is not recommended.
- Patients with a history of Mobitz Type II second-degree AV block or higher-grade AV block, sick-sinus syndrome, or sino-atrial heart block.
- Patients with a history of recurrent syncope or symptomatic bradycardia.

- Patients receiving concurrent therapy with drugs that decrease HR (eg, beta-blockers, nondihydropyridine calcium channel blockers [diltiazem and verapamil], and other drugs that may decrease HR, such as digoxin); the need to switch to non-HR-lowering medicinal products should be considered. Concomitant use of these medicinal products during ponesimod treatment initiation may be associated with severe bradycardia and heart block.

Ponesimod is contraindicated in patients who have experienced myocardial infarction, unstable angina, stroke, TIA, decompensated heart failure requiring hospitalization, or NYHA Class III or IV heart failure in the last 6 months and in patients who have presence of Mobitz type II second-degree AV block, third-degree AV block, or sick-sinus syndrome, unless the patient has a functioning pacemaker.

Caution should be applied when ponesimod is initiated in patients receiving treatment with a beta-blocker because of the additive effects on lowering HR; temporary interruption of the beta-blocker treatment may be needed prior to initiation of ponesimod. For patients receiving a stable dose of a beta-blocker, the resting HR should be considered before introducing ponesimod treatment. If the resting HR is >55 bpm under chronic beta-blocker treatment, ponesimod can be introduced. If resting HR is ≤55 bpm, beta-blocker treatment should be interrupted until the baseline HR is >55 bpm. Treatment with ponesimod can then be initiated and treatment with a beta-blocker can be re-initiated after ponesimod has been up-titrated to the target maintenance dose. Beta-blocker treatment can be initiated in patients receiving stable doses of ponesimod.

Additional risk minimization measures for this important identified risk are described in Section V.2.

Impact on the Risk-Benefit Balance of the Product:

Bradyarrhythmia occurring post-first dose is substantially mitigated through gradual up-titration of ponesimod. The SmPC and PL, as well as the educational materials for HCPs and patients/caregivers, provide information on how to manage the risk. Overall, the risk-benefit balance for the product is positive considering the severity of the disease treated and the potential efficacy for patients treated with ponesimod.

Public Health Impact:

Considering the relatively small number of patients in the target population and the substantial reduction of the known S1P bradyarrhythmia effects occurring post-first dose when ponesimod therapy is initiated with a gradual up-titration in patients without cardiac comorbidities, the impact on public health is expected to be low.

Annex 1 MedDRA Term:

Bradyarrhythmia (PT)

Important Identified Risk: Macular edema

Potential Mechanisms:

S1P contributes to regulation of vascular permeability by modulating intercellular junctions and the interaction between the cellular cytoskeleton and the extracellular matrix. Downregulation of $S1P_1$ in the context of confounding factors could be the cause of macular edema (Bigaud 2014, Camm 2014).

Evidence Source(s) and Strength of Evidence:

Cases of macular edema associated with changes in visual acuity have been reported in subjects treated with ponesimod during the clinical development program and macular edema was identified as an adverse reaction. This adverse reaction is described in the SmPC.

Characterization of the Risk:

Frequency, Seriousness, Outcomes, and Severity of Macular Edema in Clinical Trials

	All Randomized Double-blind (RDB) Population[1]		All Randomized (R) Population[2]		All Clinical Trials (CT) Population[3]
	Ponesimod (N=906) n (%)	Placebo (N=121) n (%)	Ponesimod (N=1,000) n (%)	Teriflunomide 14 mg (N=566) n (%)	Ponesimod (N=1,438) n (%)
Patients with at least one event	9 (1.0)	1 (0.8)	13 (1.3)	1 (0.2)	22 (1.5)
Relative Risk of Ponesimod versus Reference (95% CI)		1.202 (0.154 - 9.405)		7.358 (0.965 - 56.099)	
Seriousness/Outcome[4]					
Leading to discontinuation	6 (0.7)	0	8 (0.8)	0	13 (0.9)
Serious	3 (0.3)	0	5 (0.5)	0	6 (0.4)
Fatal outcome	0	0	0	0	0
Recovered	6 (0.7)	1 (0.8)	8 (0.8)	0	14 (1.0)
Recovered with sequelae	1 (0.1)	0	2 (0.2)	0	3 (0.2)
Not recovered	2 (0.2)	0	2 (0.2)	1 (0.2)	3 (0.2)
Missing	0	0	1 (0.1)	0	2 (0.1)
Number of recurrent events	10	1	15	1	24
Patient-years (PY) of exposure	417.1	54.8	1,775.8	1,079.1	4,990.9
Event Rate per 100-PY	2.4	1.8	0.8	0.1	0.5
Observed events[4,5]					
Macular oedema	7 (0.8)	1 (0.8)	10 (1.0)	0	14 (1.0)
Papilloedema	2 (0.2)	0	2 (0.2)	0	5 (0.3)
Cystoid macular oedema	0	0	0	0	1 (0.1)
Macular cyst	0	0	0	0	1 (0.1)
Macular hole	0	0	1 (0.1)	1 (0.2)	1 (0.1)
Severity (worst)[4]					
Mild	4 (0.4)	1 (0.8)	5 (0.5)	1 (0.2)	11 (0.8)
Moderate	4 (0.4)	0	5 (0.5)	0	8 (0.6)
Severe	1 (0.1)	0	3 (0.3)	0	3 (0.2)
Missing	0	0	0	0	0

Frequency, Seriousness, Outcomes, and Severity of Macular Edema in Clinical Trials

	All Randomized Double-blind (RDB) Population[1]		All Randomized (R) Population[2]		All Clinical Trials (CT) Population[3]
	Ponesimod (N=906) n (%)	Placebo (N=121) n (%)	Ponesimod (N=1,000) n (%)	Teriflunomide 14 mg (N=566) n (%)	Ponesimod (N=1,438) n (%)

[1] Trials included in the All Randomized Double-blind (RDB) Clinical Trials Population are AC-058B201 (24-week double-blind placebo control phase) and AC-058B301 (108-week double-blind active control phase, exposure up to 24 weeks).

[2] Trials included in the All Randomized (R) Clinical Trials Population are AC-058B201 (24-week double-blind placebo control phase), AC-058B301 (108-week double-blind active control phase), and AC-058B202 treatment period 1 (TP1).

[3] Trials included in the All Clinical Trials (CT) Population are AC-058B201 (24-week double-blind placebo control phase), AC-058B301 (108-week double-blind active control phase), AC-058B202 treatment periods (up to data cutoff date 18 March 2020; investigator and subject blind until the end of TP2), and AC-058B303 (open-label phase up to data cutoff date: 18 March 2020). Period of planned pregnancy interruptions excluded.

[4] A subject is counted only once regardless of the number of events within each of the categories for "Seriousness/Outcome", within the PT, and within the worst severity as applicable for the 3 related summaries.

[5] PTs are sorted by descending order of frequency in the CT Population, and in alphabetical order when more than one PT has the same frequency.

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Note: The risk of macular edema is characterized by treatment-emergent macular edema AESIs. An independent Ophthalmology Safety Board (OSB) reviewed in a blinded fashion any reports of macular edema AESIs (ie, any suspected case of macular edema) in the ponesimod clinical development program to either confirm or to rule out the diagnosis of macular edema. For data on treatment-emergent macular edema AESIs, including all suspected cases of macular edema (ie, either confirmed or ruled out as diagnosis of macular edema) in the RDB, R, and CT populations, see the table above. MedDRA terms are listed in Annex 7.3.

A total of 22 ponesimod-treated subjects in the CT population reported a suspected macular edema AESI. The OSB confirmed diagnosis of macular edema in 12 subjects (11 subjects with PT of macular edema and 1 subject with PT of cystoid macular edema). Among the 12 subjects with a confirmed diagnosis of macular edema, 2 subjects experienced 2 events of macular edema each. All of these events resolved (with or without sequelae). In 3 subjects, macular edema was reported as resolved with sequelae (not specified). According to the OSB evaluation, there was a complete resolution of edema in 2 subjects.

Among the 12 subjects with a confirmed diagnosis of macular edema, 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 edema.

Overall, most cases occurred within the first 6 months after ponesimod treatment initiation. All subjects who had macular edema onset beyond 1 year of ponesimod exposure had confounding factors (ie, optic nerve atrophy, altered vitreoretinal interface, or diabetes mellitus).

Macular edema can lead to a decline in visual acuity and a lower vision-related quality of life. Macular edema can be readily detected by appropriate clinical examinations and subsequent discontinuation of ponesimod therapy has shown to result in resolution of the condition without long-term visual impairment. Continuation of ponesimod therapy in patients with macular edema has not been evaluated. A decision on whether ponesimod should be discontinued should take into account the potential benefits and risks for the individual patient.

Risk Factors and Risk Groups:

Patients with a history of uveitis and patients with diabetes mellitus are at increased risk of developing macular edema during therapy with S1P receptor modulators.

Preventability:

An ophthalmic evaluation of the fundus, including the macula, is recommended in all patients before treatment initiation with ponesimod and again at any time if a patient reports any change in vision while on ponesimod therapy. Ponesimod therapy should not be initiated in patients with macular edema until resolution. Patients who present with visual symptoms of macular edema should be evaluated and, if confirmed, treatment with ponesimod should be discontinued. A decision on whether ponesimod should be re-initiated after resolution needs to take into account the potential benefits and risks for the individual patient.

Patients with a history of uveitis and patients with diabetes mellitus should have regular examinations of the fundus, including the macula, prior to treatment initiation with ponesimod, and have follow-up examinations while receiving therapy.

Additional risk minimization measures for this important identified risk are described in Section V.2.

Impact on the Risk-Benefit Balance of the Product:

Although macular edema occurred in subjects who received ponesimod in the clinical development program, the observed incidence was low and the events resolved after study treatment discontinuation. The SmPC and PL, as well as the educational materials for HCPs and patients/caregivers, provide information on how to manage the risk. Overall, the risk-benefit balance for the product is positive considering the severity of the disease treated and the potential efficacy for patients treated with ponesimod.

Public Health Impact:

Considering the relatively small number of patients in the target population, the relatively small number of events of macular edema reported in ponesimod clinical trials, and the reversibility of macula edema following discontinuation of ponesimod treatment, the impact on public health is expected to be low.

Annex 1 MedDRA Term:

Macular oedema (PT)

Important Identified Risk: Bronchoconstriction

Potential Mechanisms:

Increased pulmonary vascular permeability is a known class effect of $S1P_1$ receptor modulators (Oo 2011, Bigaud 2016). Mechanistic studies in rats confirmed that a single dose of ponesimod led to increased Evans blue extravasation, a marker for pulmonary vascular permeability, and increased lung weight, which was related to the increased vascular permeability. The increased permeability is expected to increase lung weights as the result of fluid accumulation.

Evidence Source(s) and Strength of Evidence:

In rats, a dose- and time-dependent effect on respiratory function was seen. The functional effect was characterized by a decrease in the relaxation time with a slight increase in the peak expiratory flow and tidal volume (increase in Penh), which indicates a transition from passive to more active expiration.

AEs suggestive of bronchoconstriction and changes in pulmonary function in the form of a decrease in FEV_1 have been reported in subjects treated with ponesimod during the clinical development program. Dyspnea and cough were identified as adverse reactions. These findings and adverse reactions are described in the SmPC.

Characterization of the Risk:

Frequency, Seriousness, Outcomes, and Severity of Bronchoconstriction in Clinical Trials

	All Randomized Double-blind (RDB) Population[1]		All Randomized (R) Population[2]		All Clinical Trials (CT) Population[3]
	Ponesimod (N=906) n (%)	Placebo (N=121) n (%)	Ponesimod (N=1,000) n (%)	Teriflunomide 14 mg (N=566) n (%)	Ponesimod (N=1,438) n (%)
Patients with at least one event	91 (10.0)	6 (5.0)	132 (13.2)	15 (2.7)	218 (15.2)
Relative Risk of Ponesimod versus Reference (95% CI)		2.026 (0.906 - 4.526)		4.981 (2.949 - 8.411)	
Seriousness/Outcome[4]					
Leading to discontinuation	16 (1.8)	0	20 (2.0)	0	31 (2.2)
Serious	3 (0.3)	0	3 (0.3)	1 (0.2)	3 (0.2)
Fatal outcome	0	0	0	0	0
Recovered	67 (7.4)	4 (3.3)	104 (10.4)	10 (1.8)	163 (11.3)
Recovered with sequelae	4 (0.4)	0	6 (0.6)	1 (0.2)	6 (0.4)
Not recovered	24 (2.6)	2 (1.7)	17 (1.7)	4 (0.7)	24 (1.7)
Missing	0	0	10 (1.0)	0	57 (4.0)
Number of recurrent events	120	7	178	18	332
Patient-years (PY) of exposure	417.1	54.8	1,775.8	1,079.1	4,990.9
Event Rate per 100-PY	28.8	12.8	10.0	1.7	6.7
Observed events[4,5]					
Dyspnoea	56 (6.2)	4 (3.3)	67 (6.7)	7 (1.2)	86 (6.0)
Forced expiratory volume decreased	8 (0.9)	0	17 (1.7)	2 (0.4)	43 (3.0)
Obstructive airways disorder	8 (0.9)	1 (0.8)	19 (1.9)	0	35 (2.4)
Asthma	5 (0.6)	1 (0.8)	11 (1.1)	2 (0.4)	31 (2.2)
Forced vital capacity decreased	6 (0.7)	0	7 (0.7)	1 (0.2)	17 (1.2)
Pulmonary function test decreased	7 (0.8)	0	10 (1.0)	1 (0.2)	17 (1.2)
Dyspnoea exertional	4 (0.4)	0	6 (0.6)	0	8 (0.6)
Bronchial obstruction	2 (0.2)	0	4 (0.4)	0	7 (0.5)
Dyspnoea at rest	4 (0.4)	0	4 (0.4)	0	5 (0.3)
Bronchospasm	1 (0.1)	0	1 (0.1)	0	3 (0.2)
Wheezing	2 (0.2)	0	2 (0.2)	0	3 (0.2)
Allergic respiratory symptom	0	0	1 (0.1)	1 (0.2)	1 (0.1)
Bronchial hyperreactivity	0	0	0	0	1 (0.1)
Carbon monoxide diffusing capacity decreased	1 (0.1)	0	1 (0.1)	0	1 (0.1)
Pulmonary function test abnormal	0	0	0	0	1 (0.1)
Hyperventilation	0	0	0	1 (0.2)	0
Interstitial lung disease	0	0	0	1 (0.2)	0

Frequency, Seriousness, Outcomes, and Severity of Bronchoconstriction in Clinical Trials

	All Randomized Double-blind (RDB) Population[1]		All Randomized (R) Population[2]		All Clinical Trials (CT) Population[3]
	Ponesimod (N=906) n (%)	Placebo (N=121) n (%)	Ponesimod (N=1,000) n (%)	Teriflunomide 14 mg (N=566) n (%)	Ponesimod (N=1,438) n (%)
Severity (worst)[4]					
Mild	51 (5.6)	4 (3.3)	81 (8.1)	10 (1.8)	147 (10.2)
Moderate	36 (4.0)	2 (1.7)	46 (4.6)	5 (0.9)	65 (4.5)
Severe	3 (0.3)	0	4 (0.4)	0	5 (0.3)
Missing	1 (0.1)	0	1 (0.1)	0	1 (0.1)

[1] Trials included in the All Randomized Double-blind (RDB) Clinical Trials Population are AC-058B201 (24-week double-blind placebo control phase) and AC-058B301 (108-week double-blind active control phase, exposure up to 24 weeks).

[2] Trials included in the All Randomized (R) Clinical Trials Population are AC-058B201 (24-week double-blind placebo control phase), AC-058B301 (108-week double-blind active control phase), and AC-058B202 treatment period 1 (TP1).

[3] Trials included in the All Clinical Trials (CT) Population are AC-058B201 (24-week double-blind placebo control phase), AC-058B301 (108-week double-blind active control phase), AC-058B202 treatment periods (up to data cutoff date 18 March 2020; investigator and subject blind until the end of TP2), and AC-058B303 (open-label phase up to data cutoff date: 18 March 2020). Period of planned pregnancy interruptions excluded.

[4] A subject is counted only once regardless of the number of events within each of the categories for "Seriousness/Outcome", within the PT, and within the worst severity as applicable for the 3 related summaries.

[5] PTs are sorted by descending order of frequency in the CT Population, and in alphabetical order when more than one PT has the same frequency.

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The risk of bronchoconstriction is characterized by treatment-emergent pulmonary AESIs. For data on treatment-emergent pulmonary AESIs in the RDB, R, and CT populations, see the table above. MedDRA terms are listed in Annex 7.3.

In Trial B301, a higher proportion of subjects in the ponesimod 20-mg group (8.0%) compared to subjects in the teriflunomide 14-mg group (2.7%) had a pulmonary AESI. Most first events in the ponesimod 20-mg group were observed during the first 12 weeks. The most frequently reported PT was dyspnea. Premature study treatment discontinuation due to pulmonary AESIs was only reported in the ponesimod 20-mg group (7 subjects, 1.2%). These included dyspnea in 6 subjects (1.1%). A total of 3 subjects (2 on ponesimod 20 mg and 1 on teriflunomide 14 mg) had treatment-emergent pulmonary serious adverse events (SAEs). One subject on ponesimod had an SAE of bronchospasm and a non-serious AE of dyspnea on Day 30. The subject was hospitalized to rule out cardiac origin of dyspnea. Both events were reported as recovered/resolved on Day 143. The events were considered related to study drug by the investigator and study drug was withdrawn. The other subject on ponesimod had an SAE of bronchial asthma on Day 47. The subject was hospitalized for diagnostic process due to exertional dyspnea. The event was reported as recovered/resolved with sequelae on Day 74 and was considered related to study drug by the investigator. No action towards study drug was taken due to this event.

In Trial B201, pulmonary AESIs were reported in 8.3% of subjects in the ponesimod 10-mg group, 12.3% of subjects in the ponesimod 20-mg group, and 24.4% of subjects in the ponesimod 40-mg

group compared to 5.0% in the placebo group. Most of the AEs were reported within the first 4 weeks of treatment. The most commonly reported PT was dyspnea.

During Analysis Period 1[3] (AP1) of Trials B201/B202, a dose-related trend was observed in the incidence of pulmonary AESIs in the 10-, 20-, and 40-mg dose groups (9.4%, 17.9%, 32.5%, respectively; exposure-adjusted incidence: 8.8, 12.9, and 32.0 per 100 subject-years, respectively). In particular, the incidence of dyspnea was higher in the 40-mg group (13.9%) compared with the 10-mg and 20-mg groups (5.0% and 6.2%, respectively).

During the interval between the data cutoff dates of 18 March 2019 and 18 March 2020 in Trial B202 and of 30 May 2019 and 18 March 2020 in Trial B303, an additional 10 subjects across the ponesimod treatment groups experienced 1 or more new pulmonary AESIs. Three subjects reported at least 1 or more pulmonary AESI leading to premature discontinuation of study treatment. None of the new events reported were assessed by the investigator as serious AESIs.

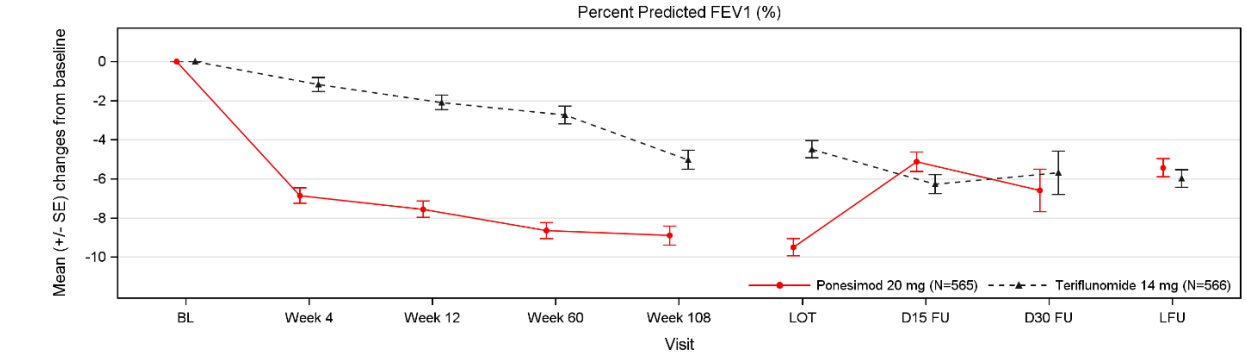
Overall, incidences of pulmonary AESIs at different dose levels indicated that the effect of ponesimod on pulmonary function was similar at the ponesimod 10-mg and 20-mg dose levels, but markedly worse at the 40-mg dose level.

In Trial B301, mean absolute decreases from baseline in %predFEV$_1$ were observed in both treatment groups (see figure below). In the ponesimod 20-mg group, there was a rapid decrease from baseline to Week 4 in %predFEV$_1$ (-6.85%) compared to a less pronounced decrease in the teriflunomide 14-mg group (-1.17%). The percent reduction from baseline in mean %predFEV$_1$ was -8.1% at Week 60 and -8.3% at Week 108 in the ponesimod 20-mg group, compared to -2.3% and -4.4%, respectively, in the teriflunomide 14-mg group. The effect of Ponesimod on FVC was less pronounced compared to its effect on FEV$_1$. The mean absolute decrease from baseline to Week 4 in percent predicted forced vital capacity (%predFVC) was -1.87% in the ponesimod 20-mg group and -0.64% in the teriflunomide 14-mg group. The maximum reduction from baseline in mean %predFVC was observed at Week 12 (-3.15%) and Week 108 (-3.39%) in the ponesimod 20-mg group compared to -1.61% and -3.55%, respectively, in the teriflunomide 14-mg group.

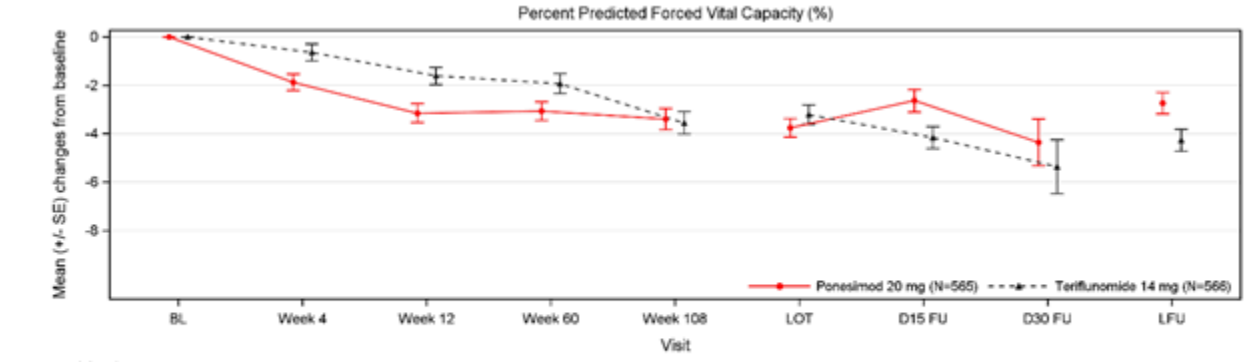
During follow-up, mean absolute changes from baseline in %predFEV$_1$ and %predFVC in the ponesimod 20-mg group were similar to those in the teriflunomide 14-mg group. At last follow-up, mean absolute decreases from baseline in %predFEV$_1$ and %predFVC were -5.43% and -2.74%, respectively in the ponesimod 20-mg group and -5.98% and -4.27%, respectively in the teriflunomide 14-mg group, indicating at least partial reversibility of the effect on pulmonary function upon study treatment discontinuation as assessed on follow-up Day 15.

[3] Analysis Period 1 includes cumulative data starting from the treatment initiation in Trial B201 up to the end of TP1 in Trial B202.

Mean (plus/minus SE) Absolute Changes From Baseline in Percent Predicted FEV_1 and FVC Results by Visit (Trial B301)



Number of Subjects									
Ponesimod 20 mg	560	533	534	486	446	552	413	79	442
Teriflunomide 14 mg	560	544	545	484	454	556	407	84	439



Number of Subjects									
Ponesimod 20 mg	560	533	534	486	446	552	413	79	442
Teriflunomide 14 mg	560	544	545	484	454	556	407	84	439

BL=Baseline (last value prior to first study drug intake) ; LOT=Last on treatment; D15 FU=Day-15 Follow-up; D30 FU=Day-30 Follow-up; LFU=Last follow-up (Last available value assessed between 8 and 37 days after last study drug intake) ; SE=standard error.
Except for data summarized under Baseline or Follow-up, only treatment-emergent results were included.
Efforts were selected according to American Thoracic Society/European Respiratory Society 2005 task force guidelines by central overreading

The proportion of subjects with a change from baseline to last on-treatment FEV_1 of ≤-0.2 L or ≤-12% was 67.2% in the ponesimod 20-mg group and 36.7% in the teriflunomide 14-mg group. A total of 129 (out of 371, 34.8%) subjects had the change from baseline returned to >-0.2 L and >-12% at the last follow-up assessment. Similarly, a higher proportion of subjects in the ponesimod 20-mg group (19.4%) had treatment-emergent absolute changes from baseline in %predFEV_1 of <-20% compared with 10.6% in the teriflunomide 14-mg group.

In Trial B303, up to the data cutoff date of 18 March 2020, treatment-emergent absolute changes from extension baseline in %predFEV_1 of <-20% were observed in a total of 8.6% of subjects who received ponesimod 20 mg.

A DL_{CO} substudy of Trial B301 was performed, which included 271 subjects (133 in the ponesimod 20-mg group and 138 in the teriflunomide 14-mg group). Mean absolute decreases from baseline in hemoglobin-corrected percent predicted DL_{CO} were observed in the ponesimod 20-mg group at Week 4, with the largest mean decreases observed at Week 60 (-11.02%) and Week 108 (-10.35%). The magnitude of change was higher than that in the teriflunomide 14-mg group, in which the mean absolute changes from baseline up to Week 108 in hemoglobin-corrected percent predicted DL_{CO} ranged from -0.47% to 1.17%. The mean absolute decreases from baseline in percent predicted DL_{CO} in the ponesimod 20-mg group was -9.55% (n=70) and -5.49% (n=9) on follow-up Day 15 and follow-up Day 30, respectively. A higher proportion of subjects in the ponesimod 20-mg group (21.2%) had treatment-emergent absolute change from baseline in hemoglobin-corrected percent predicted DL_{CO} <-20% compared to 0.9% in the teriflunomide 14-mg group. In Trial B303, of those subjects with available data at the data cutoff date of 18 March 2020, a total of 2/93 (2.2%) subjects in the P20 mg/P20 mg group and 9/81 (11.1%) subjects in the T14 mg/P20 mg group had a treatment-emergent absolute change from extension baseline in hemoglobin-corrected percent predicted DL_{CO} <-20%.

In Trial B201, dose-dependent decreases from baseline in PFTs (FEV_1, FVC and FEV_1/FVC) were observed in the ponesimod groups, compared to no decrease in the placebo group. Most cases of PFT decrease were reported within the first 4 weeks of treatment.

During AP1 of Trials B201/B202, a dose-related increase in the proportion of subjects who experienced a >20% decrease in %predFEV_1 (18 [13%], 32 [22.4%], and 71 [47.3%] subjects in the ponesimod 10-, 20-, and 40-mg dose groups, respectively) was observed.

Overall, dose-dependent reductions in FEV_1 and reductions in DL_{CO} (assessed only for the ponesimod 20-mg dose level) were observed in ponesimod-treated subjects, mostly occurring in the first month after treatment initiation.

Expert opinion after review of the data was that dyspnea is reversible upon cessation of treatment, that pulmonary function tests, while they did not return to baseline, improved after cessation of treatment, that the magnitude of persistent reduction in FEV_1 and diffusion would not be expected to result in long-term limitation, and there is no evidence to suggest progressive deterioration.

Bronchodilator assessment was introduced in TP2 of Trial B202 to test the reversibility in case of a decrease in PFT. Administration of a bronchodilator (salbutamol/albuterol) led to an increase in the mean %predFEV_1, suggesting that bronchodilators are able to rapidly reduce the effects of ponesimod on PFT variables.

Ponesimod has been tested in MS subjects with mild to moderate preexisting lung disorders (eg, asthma or chronic obstructive pulmonary disease). The mean absolute changes in %predFEV_1 were similar in this subgroup compared to the subgroup of subjects without baseline lung disorders.

Patients may experience bronchoconstriction that could affect their quality of life. However, the majority of patients with decreased pulmonary function (FEV_1 decreased) were asymptomatic and

symptoms of dyspnea mostly resolved following ponesimod treatment discontinuation in clinical trials.

Risk Factors and Risk Groups:

No specific risk factors for bronchoconstriction have been identified.

Preventability:

Ponesimod should be used with caution in patients with severe respiratory disease, pulmonary fibrosis, and chronic obstructive pulmonary disease.

Spirometry evaluation of respiratory function should be performed during therapy with ponesimod if clinically indicated.

Additional risk minimization measures for this important identified risk are described in Section V.2.

Impact on the Risk-Benefit Balance of the Product:

Most AEs suggestive of bronchoconstriction were mild or moderate in severity, and dose-dependent reductions in FEV_1 and reductions in DL_{CO} appeared to be partially reversible after study treatment discontinuation. The SmPC and PL, as well as the educational materials for HCPs and patients/caregivers, provide information on how to manage the risk. Overall, the risk-benefit balance for the product is positive considering the severity of the disease treated and the potential efficacy for patients treated with ponesimod.

Public Health Impact:

Considering the relatively small number of patients in the target population, the reversible character of events suggestive of bronchoconstriction following discontinuation of ponesimod treatment, and the ability of bronchodilators to rapidly reduce the effects of ponesimod on PFT variables, the impact on public health is expected to be low.

Annex 1 MedDRA Term:

Bronchospasm and obstruction (high level term)

Important Identified Risk: Convulsions

Potential Mechanisms:

The mechanism by which ponesimod is associated with convulsions is unknown.

Evidence Source(s) and Strength of Evidence:

Cases of convulsions have been reported in subjects treated with ponesimod during the clinical development program and are described in the SmPC. Cases of seizure have been received from

postmarketing sources. Seizures has been identified as an adverse drug reaction for other products in the same class. Although there is insufficient evidence to determine a causal relationship between convulsions/seizures and ponesimod treatment, a causal relationship is considered at least a reasonable possibility.

Characterization of the Risk:

Frequency, Seriousness, Outcomes, and Severity of Convulsions in Clinical Trials

	All Randomized Double-blind (RDB) Population[1]		All Randomized (R) Population[2]		All Clinical Trials (CT) Population[3]
	Ponesimod (N=906) n (%)	Placebo (N=121) n (%)	Ponesimod (N=1,000) n (%)	Teriflunomide 14 mg (N=566) n (%)	Ponesimod (N=1,438) n (%)
Patients with at least one event	6 (0.7)	0	13 (1.3)	1 (0.2)	18 (1.3)
Relative Risk of Ponesimod versus Reference (95% CI)		N/A		7.358 (0.965 - 56.099)	
Seriousness/Outcome[4]					
Leading to discontinuation	1 (0.1)	0	2 (0.2)	0	2 (0.1)
Serious	1 (0.1)	0	4 (0.4)	0	8 (0.6)
Fatal outcome	0	0	0	0	0
Recovered	5 (0.6)	0	11 (1.1)	1 (0.2)	14 (1.0)
Recovered with sequelae	1 (0.1)	0	1 (0.1)	0	2 (0.1)
Not recovered	0	0	1 (0.1)	1 (0.2)	1 (0.1)
Missing	0	0	0	0	3 (0.2)
Number of recurrent events	6	0	17	2	30
Patient-years (PY) of exposure	417.1	54.8	1,775.8	1,079.1	4,990.9
Event Rate per 100-PY	1.4	0.0	1.0	0.2	0.6
Observed events[4,5]					
Seizure	0	0	4 (0.4)	0	7 (0.5)
Epilepsy	2 (0.2)	0	3 (0.3)	1 (0.2)	5 (0.3)
Partial seizures with secondary generalisation	2 (0.2)	0	3 (0.3)	0	4 (0.3)
Clonic convulsion	1 (0.1)	0	1 (0.1)	0	1 (0.1)
Generalised tonic-clonic seizure	1 (0.1)	0	1 (0.1)	1 (0.2)	1 (0.1)
Partial seizures	0	0	1 (0.1)	0	1 (0.1)
Postictal state	0	0	0	0	1 (0.1)

Frequency, Seriousness, Outcomes, and Severity of Convulsions in Clinical Trials

	All Randomized Double-blind (RDB) Population[1]		All Randomized (R) Population[2]		All Clinical Trials (CT) Population[3]
	Ponesimod (N=906) n (%)	Placebo (N=121) n (%)	Ponesimod (N=1,000) n (%)	Teriflunomide 14 mg (N=566) n (%)	Ponesimod (N=1,438) n (%)
Severity (worst)[4]					
Mild	1 (0.1)	0	1 (0.1)	0	1 (0.1)
Moderate	4 (0.4)	0	9 (0.9)	1 (0.2)	12 (0.8)
Severe	1 (0.1)	0	3 (0.3)	0	5 (0.3)
Missing	0	0	0	0	0

[1] Trials included in the All Randomized Double-blind (RDB) Clinical Trials Population are AC-058B201 (24-week double-blind placebo control phase) and AC-058B301 (108-week double-blind active control phase, exposure up to 24 weeks).

[2] Trials included in the All Randomized (R) Clinical Trials Population are AC-058B201 (24-week double-blind placebo control phase), AC-058B301 (108-week double-blind active control phase), and AC-058B202 treatment period 1 (TP1).

[3] Trials included in the All Clinical Trials (CT) Population are AC-058B201 (24-week double-blind placebo control phase), AC-058B301 (108-week double-blind active control phase), AC-058B202 treatment periods (up to data cutoff date 18 March 2020; investigator and subject blind until the end of TP2), and AC-058B303 (open-label phase up to data cutoff date: 18 March 2020). Period of planned pregnancy interruptions excluded.

[4] A subject is counted only once regardless of the number of events within each of the categories for "Seriousness/Outcome", within the PT, and within the worst severity as applicable for the 3 related summaries.

[5] PTs are sorted by descending order of frequency in the CT Population, and in alphabetical order when more than one PT has the same frequency.

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The risk of convulsions is characterized by treatment-emergent seizure AESIs. For data on treatment-emergent seizure AESIs in the RDB, R, and CT populations, see the table above. MedDRA terms are listed in Annex 7.3.

In Trial B301, 8 (1.4%) subjects in the ponesimod 20-mg group had an AESI of seizure compared to 1 (0.2%) subject in the teriflunomide 14-mg group. Of the 8 subjects in the ponesimod 20-mg group, 5 had ongoing nervous system conditions at baseline (2 had epilepsy, 1 had partial seizures with secondary generalization, 1 had hydrocephalus, and 1 had polyneuropathy). Three seizure AESIs in the ponesimod 20-mg group were reported as serious, with 1 event resulting in discontinuation of study treatment. SAEs of clonic convulsion, partial seizure with secondary generalization (both considered as not related to study drug by the investigator), and epilepsy (considered as related to study drug by the investigator) were reported in 3 subjects. Only the subject that reported the SAE of partial seizure with secondary generalization had a medical history of seizure disorder (symptomatic focal epilepsy with simple focal and secondarily generalized seizures [partial seizures with secondary generalization]). The event of clonic convulsion was reported as recovered/resolved with sequelae, and study drug was withdrawn due to the event. The event of epilepsy was reported as not recovered/not resolved, and study drug was interrupted due to the event. The event of partial seizure with secondary generalization was reported as recovered/resolved, and no action was taken with study drug due to this event.

In Trial B201, epilepsy was reported in 2 subjects in the ponesimod 20-mg group.

During AP1 of Trials B201/B202, seizure occurred at low rates. Two (1.4%) subjects in the ponesimod 10-mg group, 3 (2.1%) subjects in the 20-mg group, and none in the 40-mg group experienced a TEAE in the AESI category of seizure during AP1. Of the 5 subjects with a reported seizure AESI during AP1, 2 subjects in the 20-mg group had ongoing nervous system conditions at baseline (symptomatic epilepsy). One subject (10-mg group) had an SAE of seizure during TP1 (Day 751), which was considered related to study drug by the investigator, resolved the same day and resulted in discontinuation of study treatment. No other subjects had a seizure AESI that was serious or led to discontinuation of study treatment during AP1.

Cumulatively, since the International Birth Date up to 17 March 2023, 3 postmarketing reports of seizure which contained limited information have been received, corresponding to an estimated cumulative reporting rate of 0.43% (3 cases/685 exposed patients). One report concerned a patient with medical history of seizure.

A potential contribution of ponesimod to first occurrence or recurrence of new AESIs of seizure, or to recurrence of pre-existing seizure AESI is difficult to establish.

Convulsions can have a major impact on quality of life, affecting social and cognitive functioning, as well as activities of daily living (eg, driving and employment). Uncontrolled seizures may result in injury or death.

Risk Factors and Risk Groups:

No clear predisposing factors for convulsions could be identified.

Preventability:

Currently unknown. There is no apparent pattern for patient features that predict or prevent the occurrence of convulsions.

Additional risk minimization measures for this important identified risk are described in Section V.2.

Impact on the Risk-Benefit Balance of the Product:

Although convulsions occurred in subjects who received ponesimod in the clinical development program, the observed incidence was low. Most cases were mild or moderate in severity, and some cases occurred in subjects with ongoing nervous system conditions at baseline. As convulsions occur at a higher incidence in the MS population, the contribution of ponesimod to these events is unknown. The PL and the educational materials for HCPs and patients/caregivers provide information on how to manage the risk. Overall, the risk-benefit balance for the product is positive considering the severity of the disease treated and the potential efficacy for patients treated with ponesimod.

Public Health Impact:

Considering the relatively small number of patients in the target population and the number of events of convulsion reported in ponesimod clinical trials, the impact on public health is expected to be low. This is supported by the cumulative postmarketing reporting rate to 17 March 2023 for seizure of 0.43%.

Annex 1 MedDRA Term:

Convulsions (SMQ narrow scope)

Important Potential Risk: Severe liver injury

Potential Mechanisms:

The mechanism by which ponesimod is associated with severe liver injury is unknown.

Evidence Source(s) and Strength of Evidence:

As seen with other S1P receptor modulators (Gilenya [fingolimod] SmPC 2020, Mayzent [siponimod] SmPC 2020, Zeposia [ozanimod] SmPC 2020), liver enzyme elevations, such as increased ALT and AST, have been reported in subjects treated with ponesimod during the clinical development program and were identified as adverse reactions. These adverse reactions are described in the SmPC.

Overall, the majority of ALT and AST elevations occurred within 6 or 12 months after ponesimod treatment initiation. There were no Hy's law cases in the ponesimod clinical program. Most cases of ALT increases ≥3xULN were single transient asymptomatic episodes and resolved on continued ponesimod treatment; the rest resolved upon study treatment discontinuation.

Characterization of the Risk:

Frequency, Seriousness, Outcomes, and Severity of Severe Liver Injury in Clinical Trials

	All Randomized Double-blind (RDB) Population[1]		All Randomized (R) Population[2]		All Clinical Trials (CT) Population[3]
	Ponesimod (N=906) n (%)	Placebo (N=121) n (%)	Ponesimod (N=1,000) n (%)	Teriflunomide 14 mg (N=566) n (%)	Ponesimod (N=1,438) n (%)
Patients with at least one event	4 (0.4)	0	6 (0.6)	5 (0.9)	13 (0.9)
Relative Risk of Ponesimod versus Reference (95% CI)		N/A		0.679 (0.208 - 2.216)	
Seriousness/Outcome[4]					
Leading to discontinuation	2 (0.2)	0	2 (0.2)	1 (0.2)	4 (0.3)
Serious	1 (0.1)	0	1 (0.1)	0	2 (0.1)
Fatal outcome	0	0	0	0	0
Recovered	2 (0.2)	0	4 (0.4)	4 (0.7)	10 (0.7)

Frequency, Seriousness, Outcomes, and Severity of Severe Liver Injury in Clinical Trials

	All Randomized Double-blind (RDB) Population[1]		All Randomized (R) Population[2]		All Clinical Trials (CT) Population[3]
	Ponesimod (N=906) n (%)	Placebo (N=121) n (%)	Ponesimod (N=1,000) n (%)	Teriflunomide 14 mg (N=566) n (%)	Ponesimod (N=1,438) n (%)
Recovered with sequelae	1 (0.1)	0	1 (0.1)	0	1 (0.1)
Not recovered	1 (0.1)	0	1 (0.1)	1 (0.2)	1 (0.1)
Missing	0	0	0	0	1 (0.1)
Number of recurrent events	4	0	6	5	13
Patient-Years (PY) of exposure	417.1	54.8	1,775.8	1,079.1	4,990.9
Event Rate per 100 PY	1.0	0.0	0.3	0.5	0.3
Observed events[4,5]					
Drug-induced liver injury	2 (0.2)	0	3 (0.3)	1 (0.2)	5 (0.3)
Hepatocellular injury	0	0	0	1 (0.2)	3 (0.2)
Liver disorder	1 (0.1)	0	1 (0.1)	1 (0.2)	2 (0.1)
Non-alcoholic steatohepatitis	1 (0.1)	0	1 (0.1)	0	2 (0.1)
Hepatic fibrosis	0	0	1 (0.1)	0	1 (0.1)
Hepatotoxicity	0	0	0	1 (0.2)	0
Portal hypertensive gastropathy	0	0	0	1 (0.2)	0
Severity (worst)[4]					
Mild	1 (0.1)	0	1 (0.1)	3 (0.5)	4 (0.3)
Moderate	1 (0.1)	0	3 (0.3)	2 (0.4)	6 (0.4)
Severe	2 (0.2)	0	2 (0.2)	0	3 (0.2)
Missing	0	0	0	0	0

[1] Trials included in the All Randomized, Double-blind (RDB) Clinical Trials Population are AC-058B201 (24-week double-blind placebo control phase) and AC-058B301 (108-week double-blind active control phase, exposure up to 24 weeks).

[2] Trials included in the All Randomized (R) Clinical Trials Population are AC-058B201 (24-week double-blind placebo control phase), AC-058B301 (108-week double-blind active control phase) and AC-058B202 treatment period 1 (TP1).

[3] Trials included in the All Clinical Trials (CT) Population are AC-058B201 (24-week double-blind placebo control phase), AC-058B301 (108-week double-blind active control phase), AC-058B202 treatment periods (up to data cutoff date 18 March 2020; investigator and subject blind until the end of TP2), and AC-058B303 (open-label phase up to data cutoff date: 18 March 2020). Period of planned pregnancy interruptions excluded.

[4] A subject is counted only once regardless of the number of events within each of the categories for "Seriousness/Outcome", within the PT, within the worst severity as applicable for the 3 related summaries.

[5] PTs are sorted by descending order of frequency in the CT Population, and alphabetical order when more than one PT has the same frequency.

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For data on TEAEs addressing the risk of severe liver injury in the RDB, R, and CT populations, see the table above. MedDRA terms are listed in Annex 7.3.

Of the 13 subjects in the CT population who reported at least 1 TEAE suggestive of liver injury, 2 subjects had a treatment-emergent SAE. One subject had an SAE of drug-induced liver injury, which was temporarily associated with acute viral hepatitis E; the other subject had an SAE of

hepatocellular injury temporarily associated with hepatitis B. Both SAEs led to study treatment discontinuation and resolved. There were no fatal cases and no Hy's law cases.

Seven subjects who reported a TEAE suggestive of liver injury had concurrent medical conditions or used concomitant medication associated with liver injury.

In 11 of the 13 subjects with a TEAE suggestive of liver injury, the event resolved. Of the 11 subjects who recovered, all except 2 subjects (ie, with drug-induced liver injury temporally associated with hepatitis E and with cholelithiasis/urolithiasis, respectively), had asymptomatic liver transaminase elevations in the absence of bilirubin increase, that either resolved on treatment or after treatment discontinuation. Study treatment was discontinued in 4 subjects (2 subjects with SAEs described above, 1 subject with an AE of hepatocellular injury, 1 subject with an AE of liver disorder), was interrupted in 1 subject (AE of drug-induced liver injury), and remained unchanged in 4 subjects (2 subjects with an AE of drug-induced liver injury, 1 subject with an AE of hepatocellular injury, 1 subject with an AE of liver disorder). Two subjects were no longer receiving study treatment. Another 2 subjects had an AE of non-alcoholic steatohepatitis (1 did not resolve, 1 with missing outcome); both were associated with dyslipidemia.

Liver abnormalities are generally asymptomatic, transient liver enzyme elevations. However, drug-induced liver injury could be serious and potentially fatal or require liver transplant. Considering that no Hy's law cases or drug-induced liver injury cases of concern occurred, the impact on quality of life is expected to be limited.

Risk Factors and Risk Groups:

No specific risk factors for severe liver injury have been identified.

Preventability:

Ponesimod is contraindicated in patients with moderate or severe hepatic impairment (Child Pugh class B and C, respectively).

Before initiation of treatment with ponesimod, recent (ie, within the last 6 months) transaminase and bilirubin levels should be reviewed.

Patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, rash with eosinophilia, or jaundice and/or dark urine during treatment, should be monitored for hepatotoxicity. Ponesimod should be discontinued if significant liver injury is confirmed (eg, ALT exceeds 3xULN and total bilirubin 2xULN).

Although there are no data to establish that patients with pre-existing liver disease are at increased risk to develop elevated liver function test values when taking ponesimod, caution should be exercised when using ponesimod in patients with a history of significant liver disease.

Additional risk minimization measures for this important identified risk are described in Section V.2.

Impact on the Risk-Benefit Balance of the Product:

Most TEAEs suggestive of liver injury were mild or moderate in severity and resolved during ponesimod treatment or after treatment discontinuation. Severe and serious events were confounded by concurrent medical conditions. The SmPC and PL, as well as the educational materials for HCPs and patients/caregivers, provide information on how to manage the risk. Overall, the risk-benefit balance for the product is positive considering the severity of the disease treated and the potential efficacy for patients treated with ponesimod.

Public Health Impact:

Considering the benign and transient character of liver enzyme elevations and the absence of liver events of concern in the clinical trials with ponesimod, the impact on public health is expected to be low.

Annex 1 MedDRA Term:

Drug related hepatic disorders – comprehensive search (Standardized MedDRA Query [SMQ])

Important Potential Risk: Serious opportunistic infections including PML

Potential Mechanisms:

Ponesimod reduces the number of circulating lymphocytes by blocking the egress of lymphocytes from lymphoid organs. This pharmacological effect might reduce immunosurveillance and increase the risk of serious opportunistic infections including PML.

Evidence Source(s) and Strength of Evidence:

Cases of infections have been reported in subjects treated with ponesimod during the clinical development program. Several types of infection were identified as adverse reactions. These findings and adverse reactions are described in the SmPC.

No cases of fatal infections have been reported in subjects treated with ponesimod during the clinical development program; however, life-threatening and rare fatal infections have been reported in association with other S1P receptor modulators (Gilenya SmPC 2020, Mayzent SmPC 2020).

Characterization of the Risk:

Frequency, Seriousness, Outcomes, and Severity of Serious Opportunistic Infections Including PML in Clinical Trials

	All Randomized Double-blind (RDB) Population[1]		All Randomized (R) Population[2]		All Clinical Trials (CT) Population[3]
	Ponesimod (N=906) n (%)	Placebo (N=121) n (%)	Ponesimod (N=1,000) n (%)	Teriflunomide 14 mg (N=566) n (%)	Ponesimod (N=1,438) n (%)
Patients with at least one event	5 (0.6)	0	18 (1.8)	8 (1.4)	40 (2.8)
Relative Risk of Ponesimod versus Reference (95% CI)		N/A		1.274 (0.557 - 2.910)	
Seriousness/Outcome[4]					
Leading to discontinuation	0	0	0	0	1 (0.1)
Serious	1 (0.1)	0	1 (0.1)	0	2 (0.1)
Fatal outcome	0	0	0	0	0
Recovered	5 (0.6)	0	17 (1.7)	8 (1.4)	35 (2.4)
Recovered with sequelae	0	0	1 (0.1)	0	3 (0.2)
Not recovered	0	0	0	0	1 (0.1)
Missing	0	0	0	0	1 (0.1)
Number of recurrent events	6	0	25	10	49
Patient-Years (PY) of exposure	417.1	54.8	1,775.8	1,079.1	4,990.9
Event Rate per 100 PY	1.4	0.0	1.4	0.9	1.0
Observed events[4,5]					
Herpes zoster	4 (0.4)	0	14 (1.4)	3 (0.5)	32 (2.2)
Oral candidiasis	1 (0.1)	0	2 (0.2)	1 (0.2)	4 (0.3)
Gastrointestinal candidiasis	0	0	1 (0.1)	0	2 (0.1)
Oral fungal infection	0	0	1 (0.1)	1 (0.2)	2 (0.1)
Ophthalmic herpes zoster	0	0	0	1 (0.2)	1 (0.1)
Herpes zoster cutaneous disseminated	0	0	0	1 (0.2)	0
Herpes zoster disseminated	0	0	0	1 (0.2)	0

Frequency, Seriousness, Outcomes, and Severity of Serious Opportunistic Infections Including PML in Clinical Trials

	All Randomized Double-blind (RDB) Population[1]		All Randomized (R) Population[2]		All Clinical Trials (CT) Population[3]
	Ponesimod (N=906) n (%)	Placebo (N=121) n (%)	Ponesimod (N=1,000) n (%)	Teriflunomide 14 mg (N=566) n (%)	Ponesimod (N=1,438) n (%)
Severity (worst)[4]					
Mild	2 (0.2)	0	6 (0.6)	4 (0.7)	17 (1.2)
Moderate	2 (0.2)	0	11 (1.1)	4 (0.7)	21 (1.5)
Severe	1 (0.1)	0	1 (0.1)	0	2 (0.1)
Missing	0	0	0	0	0

[1] Trials included in the All Randomized, Double-blind (RDB) Clinical Trials Population are AC-058B201 (24-week double-blind placebo control phase) and AC-058B301 (108-week double-blind active control phase, exposure up to 24 weeks).

[2] Trials included in the All Randomized (R) Clinical Trials Population are AC-058B201 (24-week double-blind placebo control phase), AC-058B301 (108-week double-blind active control phase) and AC-058B202 treatment period 1 (TP1).

[3] Trials included in the All Clinical Trials (CT) Population are AC-058B201 (24-week double-blind placebo control phase), AC-058B301 (108-week double-blind active control phase), AC-058B202 treatment periods (up to data cutoff date 18 March 2020; investigator and subject blind until the end of TP2), and AC-058B303 (open-label phase up to data cutoff date: 18 March 2020). Period of planned pregnancy interruptions excluded.

[4] A subject is counted only once regardless of the number of events within each of the categories for "Seriousness/Outcome", within the PT, within the worst severity as applicable for the 3 related summaries.

[5] PTs are sorted by descending order of frequency in the CT Population, and alphabetical order when more than one PT has the same frequency.

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For data on TEAEs addressing the risk of serious opportunistic infections including PML in the RDB, R, and CT populations, see the table above. MedDRA terms are listed in Annex 7.3.

Of the 40 subjects in the CT population who reported at least 1 TEAE suggestive of a serious opportunistic infection, 33 subjects had at least 1 TEAE associated with VZV reactivation (herpes zoster in 32 subjects with recurrent episodes in 3 subjects, ophthalmic herpes zoster in 1 subject). There were no fatal cases and no disseminated cases of herpes zoster were reported. Two subjects experienced a treatment-emergent SAE of herpes zoster. Both subjects were treated with aciclovir intravenously at the hospital while study treatment remained unchanged. The SAE was considered resolved in 1 subject and was ongoing on Day 666 in the other subject. The majority of the subjects (31/33 subjects) experienced mild or moderate events. Study treatment was discontinued in 1 subject with a single nonserious TEAE of herpes zoster. The subject experienced nonserious post-herpetic neuralgia.

There were 7 subjects with at least 1 TEAE denoting candidiasis (oral candidiasis in 4 subjects, gastrointestinal candidiasis in 2 subjects, oral fungal infection in 1 subject). Only 1 subject experienced recurrent events related to candidiasis. There were no fatal cases and no SAEs were reported. All 7 subjects experienced mild or moderate events. All events resolved except for a TEAE of gastrointestinal candidiasis in 1 subject who had multiple concomitant conditions.

Cryptococcal Infections

Cases of fatal CM and disseminated cryptococcal infections have been reported with other S1P receptor modulators. No cases of CM have been reported in ponesimod-treated patients in the clinical development program.

Progressive Multifocal Leukoencephalopathy

PML is an opportunistic viral infection of the brain caused by the John Cunningham polyoma virus that typically only occurs in patients who are immunocompromised, and that usually leads to death or severe disability. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes.

No cases of PML have been reported in ponesimod-treated subjects in the clinical development program; however, PML has been reported in patients treated with an S1P receptor modulator and other MS therapies and has been associated with some risk factors (eg, immunocompromised patients, polytherapy with immunosuppressants).

If a patient develops a clinically significant infection suggestive of a serious opportunistic infection, interruption of ponesimod treatment to allow a rapid immune recovery may improve management and outcome of the infection.

Risk Factors and Risk Groups:

Patients in an immunodeficient state and those with severe active infections or active chronic infections are at increased risk for developing serious opportunistic infections including PML.

Preventability:

Ponesimod is contraindicated in patients with severe active infections, in patients with active chronic infections, and in patients in an immunodeficient state.

Before initiating treatment with ponesimod, results from a recent (ie, within 6 months or after discontinuation of prior therapy) complete blood count (CBC) with differential (including lymphocyte count) should be reviewed. Assessments of CBC with differential are also recommended periodically during treatment. Absolute lymphocyte counts $<0.2x10^9$/L, if confirmed, should lead to interruption of ponesimod therapy until the level reaches $>0.8x10^9$/L when re-initiation of ponesimod can be considered.

Initiation of treatment with ponesimod should be delayed in patients with severe active infection until resolution. Effective diagnostic and therapeutic strategies should be employed in patients with symptoms of infection while on therapy. Suspension of treatment with ponesimod should be considered if a patient develops a serious infection. In the development program, PD effects, such as lowering effects on peripheral lymphocyte count, were restored to normal within 1 week after discontinuation of ponesimod. In the B301 trial, peripheral lymphocyte counts were restored to normal within 2 weeks after discontinuation of ponesimod, which was the first time point evaluated. Vigilance for signs and symptoms of infection should be continued for 1 to 2 weeks after ponesimod is discontinued.

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 initiating treatment with ponesimod. A full course of vaccination for antibody-negative patients with varicella vaccine is recommended prior to commencing treatment with ponesimod. Treatment with ponesimod should be delayed for 4 weeks after vaccination to allow the full effect of vaccination to occur.

Physicians should be vigilant for clinical symptoms or signs of CM. Patients with symptoms or signs 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.

Physicians should be vigilant for clinical symptoms or MRI findings suggestive of PML. MRI findings may be apparent before clinical signs or symptoms. If PML is suspected, treatment with ponesimod should be suspended until PML has been excluded. If confirmed, treatment with ponesimod should be discontinued.

In patients that are taking anti-neoplastic, immune-modulating, or immunosuppressive therapies, or with a history of prior use of these medicinal products, possible unintended additive immune system effects should be considered before initiating treatment with ponesimod. When switching from medicinal products with prolonged immune effects, the half-life and mode of action of these medicinal products must be considered in order to avoid unintended additive effects on the immune system. Use of immunosuppressants may lead to an additive effect on the immune system; therefore, caution should be applied up to 1 week after the last dose of ponesimod.

The use of live attenuated vaccines may carry a risk of infection and should therefore be avoided while patients are taking ponesimod. If immunization with a live attenuated vaccine is required, ponesimod treatment should be paused from 1 week prior to 4 weeks after a planned vaccination.

Additional risk minimization measures for this important potential risk are described in Section V.2.

Impact on the Risk-Benefit Balance of the Product:

Because of its mechanism of action, ponesimod may increase the risk of serious opportunistic infections including PML. The majority of the reported TEAEs suggestive of serious opportunistic infections (VZV reactivation and candidiasis) were mild or moderate in severity, occurred as single events, and resolved during ponesimod treatment. No cases of fatal or life-threatening infections such as CM or PML have been reported in ponesimod-treated subjects. The SmPC and PL, as well as the educational materials for HCPs and patients/caregivers, provide information on how to manage the risk. Overall, the risk-benefit balance for the product is positive considering the severity of the disease treated and the potential efficacy for patients treated with ponesimod.

Public Health Impact:

Considering the relatively small number of patients in the target population, the relatively small number of AEs suggestive of serious opportunistic infections reported, and the very small number of AEs leading to ponesimod treatment discontinuation, the impact on public health is expected to be low.

Annex 1 MedDRA Term:

Opportunistic infections (SMQ narrow scope)

Important Potential Risk: Skin cancer

Potential Mechanisms:

Ponesimod reduces the number of circulating lymphocytes by blocking the egress of lymphocytes from lymphoid organs. This pharmacological effect might reduce immunosurveillance and increase the risk of malignancy.

Evidence Source(s) and Strength of Evidence:

Cases of skin cancer, including basal cell carcinoma and a case of malignant melanoma, have been reported in subjects treated with ponesimod during the clinical development program and are described in the SmPC.

An increased risk of cutaneous malignancies has been reported in association with another S1P receptor modulator (Gilenya SmPC 2020).

Characterization of the Risk:

Frequency, Seriousness, Outcomes, and Severity of Skin Cancer in Clinical Trials

	All Randomized Double-blind (RDB) Population[1]		All Randomized (R) Population[2]		All Clinical Trials (CT) Population[3]
	Ponesimod (N=904) n (%)	Placebo (N=121) n (%)	Ponesimod (N=998) n (%)	Teriflunomide 14 mg (N=566) n (%)	Ponesimod (N=1,436) n (%)
Patients with at least one event	0	0	4 (0.4)	1 (0.2)	9 (0.6)
Relative Risk of Ponesimod versus Reference (95% CI)		NE		2.269 (0.254 - 20.247)	
Seriousness/Outcome[4]					
Leading to discontinuation	0	0	0	0	0
Serious	0	0	3 (0.3)	0	5 (0.3)
Fatal outcome	0	0	0	0	0
Recovered	0	0	2 (0.2)	1 (0.2)	7 (0.5)
Recovered with sequelae	0	0	0	0	0
Not recovered	0	0	2 (0.2)	0	2 (0.1)
Missing	0	0	0	0	0
Number of recurrent events	0	0	4	1	11
Patient-years (PY) of exposure	416.1	54.8	1,771.6	1,079.1	4,983.9
Event Rate per 100-PY	0.0	0.0	0.2	0.1	0.2
Observed events[4,5]					
Basal cell carcinoma	0	0	3 (0.3)	1 (0.2)	7 (0.5)
Keratoacanthoma	0	0	0	0	1 (0.1)
Malignant melanoma	0	0	1 (0.1)	0	1 (0.1)
Neoplasm skin	0	0	0	0	1 (0.1)
Severity (worst)[4]					
Mild	0	0	1 (0.1)	0	2 (0.1)
Moderate	0	0	2 (0.2)	1 (0.2)	4 (0.3)
Severe	0	0	1 (0.1)	0	3 (0.2)
Missing	0	0	0	0	0

[1] Trials included in the All Randomized Double-blind (RDB) Clinical Trials Population are AC-058B201 (24-week double-blind placebo control phase) and AC-058B301 (108-week double-blind active control phase, exposure up to 24 weeks).

[2] Trials included in the All Randomized (R) Clinical Trials Population are AC-058B201 (24-week double-blind placebo control phase), AC-058B301 (108-week double-blind active control phase), and AC-058B202 treatment period 1 (TP1).

[3] Trials included in the All Clinical Trials (CT) Population are AC-058B201 (24-week double-blind placebo control phase), AC-058B301 (108-week double-blind active control phase), AC-058B202 treatment periods (up to data cutoff date 18 March 2020; investigator and subject blind until the end of TP2), and AC-058B303 (open-label phase up to data cutoff date: 18 March 2020). Period of planned pregnancy interruptions excluded.

[4] A subject is counted only once regardless of the number of events within each of the categories for "Seriousness/Outcome", within the PT, and within the worst severity as applicable for the 3 related summaries.

[5] PTs are sorted by descending order of frequency in the CT Population, and in alphabetical order when more than one PT has the same frequency.

Two patients with benign conditions (Dysplastic Naevus Removal) are excluded.
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The risk of skin cancer is characterized by treatment-emergent skin malignancy AESIs. For data on treatment-emergent skin malignancy AESIs in the RDB, R, and CT populations, see the table above. MedDRA terms are listed in Annex 7.3.

In Trial B301, a higher proportion of subjects in the ponesimod 20-mg group (5, 0.9%) compared to subjects in the teriflunomide 14-mg group (1, 0.2%) had an AESI of skin malignancy. Two subjects in the ponesimod 20-mg group had a serious event. Basal cell carcinoma was reported in 2 (0.4%) ponesimod-treated subjects compared with 1 (0.2%) subject receiving teriflunomide. A case of malignant melanoma was reported in the ponesimod 20-mg group, which was reported 1.9 years after initiation of ponesimod treatment in a subject with a medical history of dermatofibroma and a family history of non-melanoma malignant skin lesion.

During AP1 of Trials B201/B202, skin malignancy occurred at a low rate. One subject had a skin malignancy (basal cell carcinoma) during TP1 (onset: Day 678) in the ponesimod 10-mg group.

The impact of skin cancer on an individual patient depends on the type and extent of the cancer. Basal cell carcinoma can be completely cured by surgical excision if detected early. Other types of skin cancer, such as malignant melanoma, can be serious and result in metastatic cancer, leading to death.

Risk Factors and Risk Groups:

Patients in an immunodeficient state and patients with a history of malignancies have an increased risk of developing skin cancer. There is also well-established scientific support for an association between ultraviolet radiation and skin cancer; sunlight can also cause immunosuppression (Brin 2014).

Preventability:

Patients treated with ponesimod should be cautioned against exposure to sunlight without protection. They should not receive concomitant phototherapy with ultraviolet B (UVB) radiation or psoralen and ultraviolet A (PUVA) photochemotherapy.

Ponesimod is contraindicated in patients with active malignancies.

In patients that are taking anti-neoplastic, immune-modulating, or immunosuppressive therapies, or with a history of prior use of these medicinal products, possible unintended additive immune system effects should be considered before initiating treatment with ponesimod. When switching from medicinal products with prolonged immune effects, the half-life and mode of action of these medicinal products must be considered in order to avoid unintended additive effects on the immune system. Use of immunosuppressants may lead to an additive effect on the immune system; therefore, caution should be applied up to 1 week after the last dose of ponesimod.

Additional risk minimization measures for this important potential risk are described in Section V.2.

Impact on the Risk-Benefit Balance of the Product:

Because of its mechanism of action, ponesimod may increase the risk of skin cancer. An increased risk of cutaneous malignancies has been reported in association with another S1P receptor modulator. Although skin cancer occurred in subjects treated with ponesimod in the clinical development program, the observed incidence was low. Most cases were mild or moderate in severity and were managed with appropriate treatment. The SmPC and PL, as well as the educational materials for HCPs and patients/caregivers provide information on how to manage the risk. Overall, the risk-benefit balance for the product is positive considering the severity of the disease treated and the potential efficacy for patients treated with ponesimod.

Public Health Impact:

Considering the relatively small number of patients in the target population, the relatively small number of serious and severe events of skin cancer reported in ponesimod clinical trials, and the curability of basal cell carcinoma when detected early, the impact on public health is expected to be low.

Annex 1 MedDRA Term:

Skin malignant tumours (SMQ narrow scope)

Important Potential Risk: Non-skin malignancy

Potential Mechanisms:

Ponesimod reduces the number of circulating lymphocytes by blocking the egress of lymphocytes from lymphoid organs. This pharmacological effect might reduce immunosurveillance and increase the risk of malignancy.

Evidence Source(s) and Strength of Evidence:

Rare cases of non-skin malignant neoplasms (including solid tumors and hematologic tumors) have been reported in subjects treated with ponesimod during the clinical development program.

Characterization of the Risk:

Frequency, Seriousness, Outcomes, and Severity of Non-skin Malignancy in Clinical Trials

	All Randomized Double-blind (RDB) Population[1]		All Randomized (R) Population[2]		All Clinical Trials (CT) Population[3]
	Ponesimod (N=906) n (%)	Placebo (N=121) n (%)	Ponesimod (N=1,000) n (%)	Teriflunomide 14 mg (N=566) n (%)	Ponesimod (N=1,438) n (%)
Patients with at least one event	1 (0.1)	1 (0.8)	2 (0.2)	1 (0.2)	11 (0.8)
Relative Risk of Ponesimod versus Reference (95% CI)		0.134 (0.008 - 2.121)		1.132 (0.103 - 12.456)	
Seriousness/Outcome[4]					
Leading to discontinuation	1 (0.1)	1 (0.8)	2 (0.2)	1 (0.2)	6 (0.4)
Serious	1 (0.1)	1 (0.8)	2 (0.2)	1 (0.2)	10 (0.7)
Fatal outcome	0	0	0	0	0
Recovered	0	0	0	0	3 (0.2)
Recovered with sequelae	0	0	0	0	2 (0.1)
Not recovered	1 (0.1)	1 (0.8)	2 (0.2)	1 (0.2)	6 (0.4)
Missing	0	0	0	0	0
Number of recurrent events	1	1	2	1	11
Patient-years (PY) of exposure	417.1	54.8	1,775.8	1,079.1	4,990.9
Event Rate per 100-PY	0.2	1.8	0.1	0.1	0.2
Observed events[4,5]					
Invasive ductal breast carcinoma	0	0	0	1 (0.2)	4 (0.3)
Breast cancer	1 (0.1)	0	1 (0.1)	0	2 (0.1)
Adenocarcinoma of the cervix	0	0	0	0	1 (0.1)
B-cell lymphoma	0	0	0	0	1 (0.1)
Invasive breast carcinoma	0	0	0	0	1 (0.1)
Oesophageal adenocarcinoma	0	0	0	0	1 (0.1)
Squamous cell carcinoma of the cervix	0	0	1 (0.1)	0	1 (0.1)
Cervix carcinoma	0	1 (0.8)	0	0	0

Frequency, Seriousness, Outcomes, and Severity of Non-skin Malignancy in Clinical Trials

	All Randomized Double-blind (RDB) Population[1]		All Randomized (R) Population[2]		All Clinical Trials (CT) Population[3]
	Ponesimod (N=906) n (%)	Placebo (N=121) n (%)	Ponesimod (N=1,000) n (%)	Teriflunomide 14 mg (N=566) n (%)	Ponesimod (N=1,438) n (%)
Severity (worst)[4]					
Mild	0	0	0	0	0
Moderate	0	0	0	0	4 (0.3)
Severe	1 (0.1)	1 (0.8)	2 (0.2)	1 (0.2)	7 (0.5)
Missing	0	0	0	0	0

[1] Trials included in the All Randomized Double-blind (RDB) Clinical Trials Population are AC-058B201 (24-week double-blind placebo control phase) and AC-058B301 (108-week double-blind active control phase, exposure up to 24 weeks).

[2] Trials included in the All Randomized (R) Clinical Trials Population are AC-058B201 (24-week double-blind placebo control phase), AC-058B301 (108-week double-blind active control phase), and AC-058B202 treatment period 1 (TP1).

[3] Trials included in the All Clinical Trials (CT) Population are AC-058B201 (24-week double-blind placebo control phase), AC-058B301 (108-week double-blind active control phase), AC-058B202 treatment periods (up to data cutoff date 18 March 2020; investigator and subject blind until the end of TP2), and AC-058B303 (open-label phase up to data cutoff date: 18 March 2020). Period of planned pregnancy interruptions excluded.

[4] A subject is counted only once regardless of the number of events within each of the categories for "Seriousness/Outcome", within the PT, and within the worst severity as applicable for the 3 related summaries.

[5] PTs are sorted by descending order of frequency in the CT Population, and in alphabetical order when more than one PT has the same frequency.

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The risk of non-skin malignancy is characterized by treatment-emergent non-skin malignancy AESIs. For data on treatment-emergent non-skin malignancy AESIs in the RDB, R, and CT populations, see the table above. MedDRA terms are listed in Annex 7.3.

In Trial B301, 1 subject in each of the treatment groups had an AESI of non-skin malignancy. Both events (squamous cell carcinoma of the cervix on Day 224 in the ponesimod 20-mg group and invasive ductal breast carcinoma on Day 86 in the teriflunomide 14-mg group) were reported as serious, considered as not related to the study drug by the investigator, and led to discontinuation of study treatment. Both events were reported as not recovered/not resolved.

In Trial B201, 2 cases of malignancy were reported, 1 in the ponesimod 10-mg group (breast cancer diagnosed after 3.5 months of treatment) and 1 in the placebo group (cervix carcinoma).

During AP1 of Trials B201/B202, no additional cases of non-skin malignancy were reported in ponesimod-treated subjects, besides the case reported in Trial B201 above.

Overall, the incidence of non-skin malignancies in ponesimod-treated subjects was low. The most commonly reported non-skin malignancy types were breast cancer and cervical carcinoma, which is in line with those expected as the majority of MS patients are women, with a substantial proportion at the age typical for onset of breast cancer.

Risk Factors and Risk Groups:

Patients in an immunodeficient state and patients with a history of malignancies have an increased risk of developing non-skin malignancy.

Preventability:

Ponesimod is contraindicated in patients with active malignancies.

In patients that are taking anti-neoplastic, immune-modulating, or immunosuppressive therapies, or with a history of prior use of these medicinal products, possible unintended additive immune system effects should be considered before initiating treatment with ponesimod. When switching from medicinal products with prolonged immune effects, the half-life and mode of action of these medicinal products must be considered in order to avoid unintended additive effects on the immune system. Use of immunosuppressants may lead to an additive effect on the immune system; therefore, caution should be applied up to 1 week after the last dose of ponesimod.

There is no apparent pattern for patient features that predict or prevent non-skin malignancy.

Impact on the Risk-Benefit Balance of the Product:

Because of its mechanism of action, ponesimod may increase the risk of non-skin malignancies. The observed incidence of non-skin malignancies was low in the clinical development program and was similar in subjects treated with ponesimod and subjects treated with placebo or comparator. The nature and types of the observed non-skin malignancies (eg, breast cancer and cervical carcinoma) were in line with those expected in the target population. Overall, the risk-benefit balance for the product is positive considering the severity of the disease treated and the potential efficacy for patients treated with ponesimod.

Public Health Impact:

Considering the relatively small number of patients in the target population and the relatively small number of events of non-skin malignancy reported in ponesimod clinical trials, the impact on public health is expected to be low.

Annex 1 MedDRA Term:

Malignant or unspecified tumours (SMQ)

Important Potential Risk: Reproductive and embryofetal toxicity

Potential Mechanisms:

Published literature on S1P indicates an essential function in vascular development during embryogenesis, cardiovascular, and limb development. Consequently, the functional antagonism of $S1P_1$ would be expected to produce detrimental effects on embryofetal and pre- and postnatal development.

Evidence Source(s) and Strength of Evidence:

Reproductive and developmental studies in pregnant rats and rabbits have demonstrated ponesimod-induced developmental toxicity, including an increase in malformations (skeletal and visceral) and embryolethality. The AUC_{0-24} in rats and rabbits at the NOAEL (1 mg/kg/day in both species) are lower than the human systemic exposures at the RHD of 20 mg/day.

Ponesimod has not been studied in pregnant women. Clinical trials of ponesimod excluded pregnant and breast-feeding women. Clear recommendations how to avoid pregnancies in women of childbearing potential are described in the SmPC.

Based on human experience in patients receiving another S1P receptor modulator, postmarketing data suggest that its use is associated with an increased risk of major congenital malformations (Gilenya SmPC 2020).

Characterization of the Risk:

Up to the data lock point of this RMP, 34 pregnancy cases were reported across completed and ongoing clinical trials with ponesimod.

Of the reported pregnancy cases, fetal exposure (ie, onset of pregnancy occurring during study drug administration or within 30 days after study drug discontinuation) to ponesimod occurred in 15 cases. One case was reported in a subject on ponesimod 10 mg and resulted in induced abortion. Thirteen cases were reported in subjects on ponesimod 20 mg and had the following outcomes: abortion induced (4 cases), abortion spontaneous (3 cases), and normal newborn (6 cases). One case was reported in a subject on ponesimod 40 mg and resulted in induced abortion. In all cases, fetal exposure to ponesimod occurred during the first trimester of pregnancy.

Of the 9 reported cases of abortion, 6 were induced and 3 were spontaneous. Among all cases of abortion, the presence of postnatal fetal abnormalities was reported as unknown in 8 cases; the remaining case concerned a benign hydatidiform mole. Among the 6 cases of induced abortion, there was no evidence of fetal abnormalities antenatally in 4 cases. The reasons for induced abortion included concern for potential fetal anomaly (1 case), unwanted pregnancy (2 cases), and molar pregnancy (benign hydatidiform mole, 1 case). The reason for induced abortion was unknown in 2 cases. The proportion of spontaneous abortions in pregnancy cases with fetal exposure to ponesimod (3/15, or 20.0%) was within the range reported for the general population (14.2%-20.9%) (Wang 2004, Buss 2006) and within the range reported for the unexposed MS population (4.3%-21.1%) (Hellwig 2011, Ebrahimi 2015).

Considering the temporal association with study drug exposure, a contribution of study drug to the event of benign hydatidiform mole could not be excluded. The investigator and the company considered the pregnancy outcome as possibly related to the study drug.

Exposure to ponesimod during pregnancy could lead to serious malformations, such as major skeletal and visceral abnormalities as shown in rat and rabbit fetuses, and increases in postimplantation losses.

Risk Factors and Risk Groups:

Women of childbearing potential who do not use effective contraception are at risk.

Preventability:

Ponesimod is contraindicated in women of childbearing potential who do not use effective contraception. Before initiation of ponesimod treatment in women of childbearing potential, a negative pregnancy test result must be available, and women should be counseled on the potential for a serious risk to the fetus and the need for effective contraception during treatment with ponesimod. Because it takes approximately 1 week to eliminate ponesimod from the body after stopping treatment, the potential risk to the fetus may persist, and women must use effective contraception during this period. When stopping ponesimod therapy for planning a pregnancy, the possible return of disease activity should be considered.

Additional risk minimization measures for this important potential risk are described in Section V.2.

Impact on the Risk-Benefit Balance of the Product:

Nonclinical data for ponesimod, as well as human experience in patients receiving another S1P receptor modulator, have demonstrated teratogenic effects in offspring. The SmPC and PL, as well as the educational materials for HCPs and patients/caregivers, provide information on how to minimize the risk of reproductive and embryofetal toxicity. Overall, the risk-benefit balance for the product is positive considering the severity of the disease treated and the potential efficacy for patients treated with ponesimod.

Public Health Impact:

Considering the relatively small number of patients in the target population and stringent routine and additional risk minimization measures to address this risk, the impact on public health is expected to be low.

Annex 1 MedDRA Term:

Pregnancy and neonatal topics (SMQ narrow scope)

Important Potential Risk: Unexpected neurological or psychiatric symptoms/signs (PRES, ADEM, atypical MS relapses)

Potential Mechanisms:

Unexpected neurological or psychiatric symptoms/signs include cases for which, in the judgment of the investigator, the disability progression is unusually severe or medically unexpected and warrants specific notification (PRES, ADEM, atypical MS relapses). PRES has been associated with the use of several immunosuppressive and immunomodulating agents which can cause endothelial dysfunction, eg, cyclosporine and tacrolimus (Wong 2003).

Evidence Source(s) and Strength of Evidence:

No cases of PRES or ADEM have been reported in subjects treated with ponesimod during the clinical development program. However, rare cases of PRES have been reported in patients receiving other S1P receptor modulators (Gilenya SmPC 2020; Mayzent SmPC 2020; Zeposia SmPC 2020).

In clinical trials of another S1P receptor modulator, rare events involving the nervous system, including ischemic and hemorrhagic strokes and neurological atypical disorders such as ADEM-like events, occurred in patients treated at higher doses (Gilenya SmPC 2020).

Characterization of the Risk:

Frequency, Seriousness, Outcomes, and Severity of Unexpected Neurological or Psychiatric Symptoms/Signs (PRES, ADEM, Atypical MS Relapses) in Clinical Trials

	All Randomized Double-blind (RDB) Population[1]		**All Randomized (R) Population[2]**		**All Clinical Trials (CT) Population[3]**
	Ponesimod (N=906) n (%)	**Placebo (N=121) n (%)**	**Ponesimod (N=1,000) n (%)**	**Teriflunomide 14 mg (N=566) n (%)**	**Ponesimod (N=1,438) n (%)**
Patients with at least one event	2 (0.2)	0	2 (0.2)	1 (0.2)	6 (0.4)
Relative Risk of Ponesimod versus Reference (95% CI)		N/A		1.132 (0.103 - 12.456)	
Seriousness/Outcome[4]					
Leading to discontinuation	0	0	0	1 (0.2)	1 (0.1)
Serious	1 (0.1)	0	1 (0.1)	1 (0.2)	4 (0.3)
Fatal outcome	0	0	0	0	0
Recovered	1 (0.1)	0	1 (0.1)	0	3 (0.2)
Recovered with sequelae	1 (0.1)	0	1 (0.1)	1 (0.2)	2 (0.1)
Not recovered	0	0	0	0	0
Missing	0	0	0	0	1 (0.1)
Number of recurrent events	2	0	2	1	6
Patient-Years (PY) of exposure	417.1	54.8	1,775.8	1,079.1	4,990.9
Event Rate per 100 PY	0.5	0.0	0.1	0.1	0.1
Observed events[4,5]					
Multiple sclerosis relapse	2 (0.2)	0	2 (0.2)	1 (0.2)	6 (0.4)

Frequency, Seriousness, Outcomes, and Severity of Unexpected Neurological or Psychiatric Symptoms/Signs (PRES, ADEM, Atypical MS Relapses) in Clinical Trials

	All Randomized Double-blind (RDB) Population[1]		All Randomized (R) Population[2]		All Clinical Trials (CT) Population[3]
	Ponesimod (N=906) n (%)	Placebo (N=121) n (%)	Ponesimod (N=1,000) n (%)	Teriflunomide 14 mg (N=566) n (%)	Ponesimod (N=1,438) n (%)
Severity (worst)[4]					
Mild	0	0	0	0	0
Moderate	1 (0.1)	0	1 (0.1)	0	4 (0.3)
Severe	1 (0.1)	0	1 (0.1)	1 (0.2)	2 (0.1)
Missing	0	0	0	0	0

[1] Trials included in the All Randomized, Double-blind (RDB) Clinical Trials Population are AC-058B201 (24-week double-blind placebo control phase) and AC-058B301 (108-week double-blind active control phase, exposure up to 24 weeks).

[2] Trials included in the All Randomized (R) Clinical Trials Population are AC-058B201 (24-week double-blind placebo control phase), AC-058B301 (108-week double-blind active control phase) and AC-058B202 treatment period 1 (TP1).

[3] Trials included in the All Clinical Trials (CT) Population are AC-058B201 (24-week double-blind placebo control phase), AC-058B301 (108-week double-blind active control phase), AC-058B202 treatment periods (up to data cutoff date 18 March 2020; investigator and subject blind until the end of TP2), and AC-058B303 (open-label phase up to data cutoff date: 18 March 2020). Period of planned pregnancy interruptions excluded.

[4] A subject is counted only once regardless of the number of events within each of the categories for "Seriousness/Outcome", within the PT, within the worst severity as applicable for the 3 related summaries.

[5] PTs are sorted by descending order of frequency in the CT Population, and alphabetical order when more than one PT has the same frequency.

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For data on TEAEs addressing the risk of unexpected neurological or psychiatric symptoms/signs (PRES, ADEM, atypical MS relapses) in the RDB, R, and CT populations, see the table above. MedDRA terms are listed in Annex 7.3.

In the CT population, 6 subjects reported at least 1 TEAE of MS relapse; all were moderate (in 4 subjects) or severe (in 2 subjects) in intensity. All subjects experienced a single event, except for 1 subject who experienced 2 moderate events (dysphoria associated with unconfirmed MS relapse and numbness in leg associated with unconfirmed MS relapse) with the same start and end dates. In 4 subjects, MS relapse was reported as a treatment-emergent SAE; these events warranted specific notice due to unusual severity, prolonged hospitalization for MS relapse, atypical MRI finding, and remarkable clinical manifestations (seizure and somnolence, see below), respectively. Study treatment was discontinued in 1 subject. Five of the 6 subjects recovered, while outcome was missing for 1 subject.

The SAE of MS relapse with remarkable clinical manifestations (seizure and somnolence) was the only TEAE that was considered an atypical MS relapse by the investigator. Because a series of generalized seizures occurred 7 months after the atypical MS relapse, these seizures were assessed by the investigator as not related to the study treatment since symptomatic epilepsy was associated with structural brain changes due to MS. While this MS relapse was considered by the investigator

atypical in its presentation due to concurrent seizure, the MS relapse was accompanied by symptoms/signs (ie, seizure) that, in hindsight, were likely caused by structural brain changes due to MS. This is not unexpected as the correlation between MS and seizures is known (Sponsler 2011, Sokic 2001). This atypical MS relapse was considered related to study treatment by the investigator because the subject had not experienced atypical MS relapse presentations prior to study treatment administration.

No TEAEs of PRES or ADEM were reported in subjects treated with ponesimod during the clinical development program.

Symptoms of PRES are usually reversible but may evolve into ischemic stroke or cerebral hemorrhage. Delay in diagnosis and treatment may lead to permanent neurological sequelae. If PRES is suspected, ponesimod should be discontinued.

Risk Factors and Risk Groups:

Many patients with PRES have potentially severe comorbidities such as bone marrow or solid organ transplantation, chronic renal failure, and chronic hypertension, which may be predisposing factors. Infections and autoimmune disease have also been associated with PRES. Hypertension of renal origin has been reported to be a significant cause of PRES, and patients with renal dysfunction appear to be at higher risk of developing PRES.

Preventability:

If a patient develops any unexpected neurological or psychiatric signs or symptoms (eg, cognitive deficits, behavioral changes, cortical visual disturbances, other neurological cortical symptoms/signs), or any signs or symptoms suggestive of increased intracranial pressure or accelerated neurological deterioration, the physician should promptly schedule a complete physical and neurological examination and should consider an MRI.

Additional risk minimization measures for this important potential risk are described in Section V.2.

Impact on the Risk-Benefit Balance of the Product:

Although rare cases of PRES and ADEM-like events have been reported in patients receiving an S1P receptor modulator, such events have not been reported in ponesimod clinical trials. The SmPC and PL, as well as the educational materials for HCPs and patients/caregivers, provide information on how to manage the risk. Overall, the risk-benefit balance for the product is positive considering the severity of the disease treated and the potential efficacy for patients treated with ponesimod.

Public Health Impact:

Considering the relatively small number of patients in the target population, the small number of cases of PRES and ADEM-like events reported with other S1P receptor modulators, the absence of reports of such events in ponesimod clinical trials, as well as the reversible character of PRES and ADEM-like events following S1P receptor modulator treatment discontinuation and appropriate monitoring of patients, the impact on public health is expected to be low.

Annex 1 MedDRA Term:

Noninfectious encephalopathy/delirium (SMQ narrow scope)

SVII.3.2. Presentation of the Missing Information

Missing information: Use in elderly patients
Evidence source: Clinical trials of ponesimod did not include patients aged 65 years and older. The results from a population PK analysis indicated that age (range: 17-65 years) does not significantly influence the PK of ponesimod. However, ponesimod should be prescribed with caution in patients aged 65 years and older due to the lack of data on safety and efficacy. In general, dose selection for an elderly patient should be done cautiously, reflecting the higher frequency of decreased hepatic or cardiac function, concomitant disease, or other drug therapy.
Population in need of further characterization: Patients aged 65 years and older.

Missing information: Long-term safety of ponesimod
Evidence source: Although safety data are available for subjects treated with ponesimod for ≥10 years in clinical trials, there is a limited number of subjects with long-term exposure to ponesimod. Of the 1,438 subjects treated with ponesimod in the CT population, 849 subjects were exposed ≥2 years, 253 were exposed ≥5 years, 222 were exposed ≥8 years, 192 subjects were exposed ≥9 years, and 33 subjects were exposed ≥10 years. Long-term extension trials (B202 and B303) are ongoing to further characterize the long-term safety profile of ponesimod.
Population in need of further characterization: Patients exposed to ponesimod long term.

PART II: SAFETY SPECIFICATION

Module SVIII: Summary of the Safety Concerns

Table SVIII.1: Summary of Safety Concerns

Important Identified Risks	Bradyarrhythmia occurring post-first dose
	Macular edema
	Bronchoconstriction
	Convulsions
Important Potential Risks	Severe liver injury
	Serious opportunistic infections including PML
	Skin cancer
	Non-skin malignancy
	Reproductive and embryofetal toxicity
	Unexpected neurological or psychiatric symptoms/signs (PRES, ADEM, atypical MS relapses)
Missing Information	Use in elderly patients
	Long-term safety of ponesimod

PART III: PHARMACOVIGILANCE PLAN (Including Postauthorization Safety Studies)

III.1. Routine Pharmacovigilance Activities Beyond Adverse Reaction Reporting and Signal Detection

Specific Follow-up Questionnaires for Safety Concerns	
Safety Concern	Purpose/Description
Convulsions	Targeted follow-up questionnaire (TFUQ) to obtain structured information on reported AEs
Serious opportunistic infections including PML	TFUQ to obtain structured information on reported AEs
Unexpected neurological or psychiatric symptoms/signs (PRES, ADEM, atypical MS relapses)	TFUQ to obtain structured information on reported AEs

Other Forms of Routine Pharmacovigilance Activities		
Activity	Objective/Description	Milestones
Cumulative reviews of events of convulsion in the Periodic Benefit-Risk Evaluation Report (PBRER).	To further characterize the impact of convulsions on the safety profile of ponesimod.	Ongoing cumulative safety presentation at the end of each PBRER reporting interval.
Independent review of cases of suspected PML by an external adjudication committee.	To further characterize the important potential risk of serious opportunistic infections including PML, an external adjudication committee will review and adjudicate potential PML cases.	Ongoing safety presentation of reported cases and adjudication outcome at the end of each PBRER reporting interval.
Cumulative reviews of reports of ponesimod use in elderly patients in the PBRER.	To monitor the safety of ponesimod in patients aged 65 years and older.	Ongoing cumulative safety presentation at the end of each PBRER reporting interval.

III.2. Additional Pharmacovigilance Activities

Additional Pharmacovigilance Activities	
Study name and title	PCSNSP004001: Ponesimod Pregnancy Outcomes Program Utilizing Enhanced Pharmacovigilance Monitoring (POEM).
Rationale and study objectives	Rationale: To evaluate the potential risk of reproductive and embryofetal toxicity in pregnant women exposed to ponesimod. Objectives: 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.

Additional Pharmacovigilance Activities	
Safety concern(s) addressed	Reproductive and embryofetal toxicity
Study design	Observational, prospective study
Study population	Women exposed to ponesimod during pregnancy
Milestones	Start of data collection: 19 May 2021 End of data collection: 19 May 2031 Interim reports: 20 June 2023 (completed), 20 June 2026, and 20 June 2029 Final report: 19 May 2032
Study name and title	AC-058B303/OPTIMUM-LT - Multicenter, 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.
Rationale and study objectives	Rationale: To characterize the long-term safety of ponesimod and control of disease in subjects with RMS and to investigate the effect on disease activity in a relatively large population after a brief interruption. Objectives: 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.
Safety concern(s) addressed	• Bradyarrhythmia occurring post-first dose • Bronchoconstriction • Convulsions • Severe liver injury • Serious opportunistic infections including PML • Skin cancer • Non-skin malignancy • Unexpected neurological or psychiatric symptoms/signs (PRES, ADEM, atypical MS relapses) • Long-term safety of ponesimod
Study design	Prospective, multicenter, open-label, non-comparative, single-arm, Phase 3 long-term extension trial.
Study population	Subjects who completed the double-blind treatment in Trial B301 as scheduled.
Milestones	Start of data collection (first patient in): 13/07/2017 End of data collection (last patient last visit): 16/02/2024 Interim report: 02/03/2020 Final report: 15/02/2025

Additional Pharmacovigilance Activities	
Study name and title	AC-058B202 - Multicenter, randomized, 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.
Rationale and study objectives	Rationale: To investigate the long-term safety, tolerability, and efficacy of ponesimod. Objectives: To investigate the long-term safety and tolerability of ponesimod.
Safety concern(s) addressed	• Bronchoconstriction • Convulsions • Severe liver injury • Serious opportunistic infections including PML • Skin cancer • Non-skin malignancy • Unexpected neurological or psychiatric symptoms/signs (PRES, ADEM, atypical MS relapses) • Long-term safety of ponesimod
Study design	Prospective, multicenter, multinational, randomized, double-blind, multiple-dose, uncontrolled, parallel group extension trial.
Study population	Subjects who completed the regular end-of-treatment visit while on study treatment in Trial B201.
Milestones	Start of data collection: (first patient in): 12/05/2010 End of data collection (last patient last visit):15/12/2023 Interim report: 02/03/2020 Final report: 14/12/2024
Study name and title	PCSNSP003693: Survey to Assess the Effectiveness of Ponvory Educational Materials for Additional Risk Minimization Measures in the European Union.
Rationale and study objectives	Rationale: To assess the effectiveness of HCP and patient/caregiver educational materials (ie, healthcare professional checklist, patient/caregiver guide, and pregnancy-specific patient reminder card) aimed at minimizing important risks. Objectives: To determine the effectiveness of the educational materials related to the understanding and management of Ponvory important identified and potential risks in the European Union.

Additional Pharmacovigilance Activities	
Safety concern(s) addressed	• Bradyarrhythmia occurring post-first dose • Macular edema • Bronchoconstriction • Convulsions • Severe liver injury • Serious opportunistic infections including PML • Skin cancer • Reproductive and embryofetal toxicity • Unexpected neurological or psychiatric symptoms/signs (PRES, ADEM, atypical MS relapses)
Study design	Observational, cross-sectional study; web-based survey.
Study population	• HCPs (physicians/neurologists and MS specialist nurses) who prescribe ponesimod and/or monitor, oversee the management of, or provide in-person medical supervision of patients treated with ponesimod. • Patients who receive Ponvory (or their caregivers).
Milestones	Start of data collection: March 2024 in selected EU countries where ponesimod is marketed and reimbursed for at least 6 months. End of data collection: December 2024. Interim report: Not applicable. Periodic updates will be provided in the PBRER. Final report: December 2025 (1 year after the end of data collection).

III.3. Summary Table of Additional Pharmacovigilance Activities

Table Part III.3: Ongoing 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 authorization				
Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
PCSNSP004001 Ponesimod Pregnancy Outcomes Program Utilizing Enhanced Pharmacovigilance Monitoring (POEM) Ongoing	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 reports	20 June 2023 (completed) 20 June 2026 20 June 2029
			Final report	19 May 2032
AC-058B303/ OPTIMUM-LT Multicenter, 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 • Convulsions • Severe liver injury • Serious opportunistic infections including PML • Skin cancer • Non-skin malignancy • Unexpected neurological or psychiatric symptoms/signs (PRES, ADEM, atypical MS relapses) • Long-term safety of ponesimod	Final report	15/02/2025

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
AC-058B202 Multicenter, randomized, 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 • Convulsions • Severe liver injury • Serious opportunistic infections including PML • Skin cancer • Non-skin malignancy • Unexpected neurological or psychiatric symptoms/signs (PRES, ADEM, atypical MS relapses) • Long-term safety of ponesimod	Final report	14/12/2024
PCSNSP003693 Survey to Assess the Effectiveness of Ponvory Educational Materials for Additional Risk Minimization Measures in the European Union Planned	To determine the effectiveness of the educational materials related to the understanding and management of Ponvory important identified and potential risks in the European Union.	• Bradyarrhythmia occurring post-first dose • Macular edema • Bronchoconstriction • Convulsions • Severe liver injury • Serious opportunistic infections including PML • Skin cancer • Reproductive and embryofetal toxicity • 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	December 2025 (1 year after the end of data collection)

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

Table Part IV.1: Planned and Ongoing Postauthorization Efficacy Studies That Are Conditions of the Marketing Authorization or That Are Specific Obligations

Study Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Dates
Efficacy studies which are conditions of the marketing authorizations				
Not applicable				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				

PART V: RISK MINIMIZATION MEASURES (Including Evaluation of the Effectiveness of Risk Minimization Activities)

Risk Minimization Plan

V.1. Routine Risk Minimization Measures

Table Part V.1: Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Identified Risks	
Bradyarrhythmia occurring post-first dose	**Routine risk communication:** • 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 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • 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. • Appropriate management should be initiated in case certain post-dose heart-related disorders or symptoms occur, as described in SmPC Section 4.4.

Safety Concern	Routine Risk Minimization Activities
	• 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. **Other routine risk minimization measures beyond the Product Information:** • Pack size: ponesimod treatment initiation pack for 14-day up-titration • Legal status: medicinal product subject to restricted medical prescription
Macular edema	**Routine risk communication:** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • 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 edema until resolution, and patients with visual symptoms of macular edema 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 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 edema should call their physician immediately, as described in PL Sections 2 and 4.

Safety Concern	Routine Risk Minimization Activities
	Other routine risk minimization measures beyond the Product Information: • Legal status: medicinal product subject to restricted medical prescription
Bronchoconstriction	**Routine risk communication:** • SmPC Section 4.4 • SmPC Section 4.8 • SmPC Section 5.1 • PL Section 2 • PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • 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. **Other routine risk minimization measures beyond the Product Information:** • Legal status: medicinal product subject to restricted medical prescription
Convulsions	**Routine risk communication:** • SmPC Section 4.8 • PL Section 2 • PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Patients who experience symptoms of a seizure should call their physician immediately, as described in PL Section 2. **Other routine risk minimization measures beyond the Product Information:** • Legal status: medicinal product subject to restricted medical prescription
Important Potential Risks	
Severe liver injury	**Routine risk communication:** • SmPC Section 4.2 • SmPC Section 4.3 • SmPC Section 4.4 • SmPC Section 4.8

Safety Concern	Routine Risk Minimization Activities
	• SmPC Section 5.2 • PL Section 2 • PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • 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 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. **Other routine risk minimization measures beyond the Product Information:** • Legal status: medicinal product subject to restricted medical prescription
Serious opportunistic infections including PML	**Routine risk communication:** • SmPC Section 4.3 • SmPC Section 4.4 • SmPC Section 4.5 • SmPC Section 4.8 • PL Section 2 • PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • 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. • 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

Safety Concern	Routine Risk Minimization Activities
	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 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 immunization 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.

Safety Concern	Routine Risk Minimization Activities
	• 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. • **Other routine risk minimization measures beyond the Product Information:** Legal status: medicinal product subject to restricted medical prescription
Skin cancer	**Routine risk communication:** • SmPC Section 4.3 • SmPC Section 4.4 • SmPC Section 4.5 • SmPC Section 4.8 • PL Section 2 • PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • 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. **Other routine risk minimization measures beyond the Product Information:** • Legal status: medicinal product subject to restricted medical prescription

Safety Concern	Routine Risk Minimization Activities
Non-skin malignancy	**Routine risk communication:** • SmPC Section 4.3 • SmPC Section 4.4 • SmPC Section 4.5 • PL Section 2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • 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. **Other routine risk minimization measures beyond the Product Information:** • Legal status: medicinal product subject to restricted medical prescription
Reproductive and embryofetal toxicity	**Routine risk communication:** • SmPC Section 4.3 • SmPC Section 4.4 • SmPC Section 4.6 • SmPC Section 5.3 • PL Section 2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • 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.

Safety Concern	Routine Risk Minimization Activities
	• 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. • Patients are advised to talk to their doctor about reliable methods of contraception, as described in PL Section 2. **Other routine risk minimization measures beyond the Product Information:** • Legal status: medicinal product subject to restricted medical prescription
Unexpected neurological or psychiatric symptoms/signs (PRES, ADEM, atypical MS relapses)	**Routine risk communication:** • SmPC Section 4.4 • PL Section 2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • 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. **Other routine risk minimization measures beyond the Product Information:** • Legal status: medicinal product subject to restricted medical prescription

Safety Concern	Routine Risk Minimization Activities
Missing Information	
Use in elderly patients	**Routine risk communication:** • SmPC Section 4.2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • None **Other routine risk minimization measures beyond the Product Information:** • Legal status: medicinal product subject to restricted medical prescription
Long-term safety of ponesimod	**Routine risk communication:** • None **Routine risk minimization activities recommending specific clinical measures to address the risk:** • None **Other routine risk minimization measures beyond the Product Information:** • Legal status: medicinal product subject to restricted medical prescription

V.2. Additional Risk Minimization Measures

Additional Risk Minimization Activity 1 Healthcare professional checklist	
Objective(s):	Objectives: The aim of the healthcare professional checklist is to increase awareness of the following important risks associated with the use of ponesimod and to provide guidance on how to manage these risks: Important identified risks • Bradyarrhythmia occurring post-first dose • Macular edema • Bronchoconstriction • Convulsions Important potential risks • Severe liver injury • Serious opportunistic infections including PML • Skin cancer • Reproductive and embryofetal toxicity • Unexpected neurological or psychiatric symptoms/signs (PRES, ADEM, atypical MS relapses)
Rationale for the additional risk minimization activity:	The healthcare professional checklist is considered an essential additional measure to ensure proper screening, monitoring, diagnosis, evaluation, and management of patients at increased risk for experiencing these safety concerns.
Target audience and planned distribution path:	HCPs National communication plan (including planned distribution) will be agreed at the Member State level.
Plans to evaluate the effectiveness of the interventions and criteria for success:	Surveillance systems are used to detect safety signals based on AE reporting rates and trends. In addition, reporting trend analyses from postmarketing safety data are monitored in the PBRER. Assessments are conducted at the end of each PBRER reporting interval. Stable AE reporting rates and trends from the postmarketing safety data are the criteria for success. A survey to assess the effectiveness of the healthcare professional checklist is planned.

Additional Risk Minimization Activity 2 Patient/caregiver guide	
Objective(s):	Objectives: The aim of the patient/caregiver guide is to increase awareness of the following important risks associated with the use of ponesimod and to provide guidance on how to manage these risks: Important identified risks • Bradyarrhythmia occurring post-first dose • Macular edema • Bronchoconstriction • Convulsions Important potential risks • Severe liver injury • Serious opportunistic infections including PML • Skin cancer • Reproductive and embryofetal toxicity • Unexpected neurological or psychiatric symptoms/signs (PRES, ADEM, atypical MS relapses)
Rationale for the additional risk minimization activity:	The patient/caregiver guide, which is provided to the patient by the HCP, is considered an essential additional measure to ensure proper, safe, and effective use of the product.
Target audience and planned distribution path:	Patients/caregivers National communication plan (including planned distribution) will be agreed at the Member State level.
Plans to evaluate the effectiveness of the interventions and criteria for success:	Surveillance systems are used to detect safety signals based on AE reporting rates and trends. In addition, reporting trend analyses from postmarketing safety data are monitored in the PBRER. Assessments are conducted at the end of each PBRER reporting interval. Stable AE reporting rates and trends from postmarketing safety data are the criteria for success. A survey to assess the effectiveness of the patient/caregiver guide is planned.
Additional Risk Minimization Activity 3 Pregnancy-specific patient reminder card	
Objective(s):	Objectives: The aim of the pregnancy-specific patient reminder card is to increase awareness of the important potential risk of reproductive and embryofetal toxicity associated with the use of ponesimod in women of childbearing potential and to provide guidance on how to manage this risk.

Rationale for the additional risk minimization activity:	The pregnancy-specific patient reminder card is considered an essential additional measure to ensure that women do not become pregnant while on ponesimod or are appropriately monitored if they do become pregnant.
Target audience and planned distribution path:	Female patients of childbearing potential National communication plan (including planned distribution) will be agreed at the Member State level.
Plans to evaluate the effectiveness of the interventions and criteria for success:	Surveillance systems are used to detect safety signals based on AE reporting rates and trends. In addition, reporting trend analyses from postmarketing safety data are monitored in the PBRER. Assessments are conducted at the end of each PBRER reporting interval. Stable AE reporting rates and trends from postmarketing safety data are the criteria for success. A survey to assess the effectiveness of the pregnancy-specific patient reminder card is planned.

V.2.1. Removal of Additional Risk Minimization Activities

Activity 1	**Safety Concern(s) Addressed/Rationale for the Removal of Additional Risk Minimization Activity**
Not applicable	

V.3. Summary of Risk Minimization Measures and Pharmacovigilance Activities

Table Part V.3: Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks		
Bradyarrhythmia occurring post-first dose	**Routine risk minimization 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.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • Trial AC-058B303/ OPTIMUM-LT Final report: 15/02/2025 • PCSNSP003693 Survey to Assess the Effectiveness of Ponvory Educational Materials for Additional Risk Minimization Measures in the European Union Final report: December 2025 (1 year after the end of data collection)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	• 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. • 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.	

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	• 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 minimization measures:** • Healthcare professional checklist • Patient/caregiver guide	
Macular edema	**Routine risk minimization 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.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • PCSNSP003693 Survey to Assess the Effectiveness of Ponvory Educational Materials for Additional Risk Minimization Measures in the European Union Final report: December 2025 (1 year after the end of data collection)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	• Ponesimod therapy should not be initiated in patients with macular edema until resolution, and patients with visual symptoms of macular edema 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 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 edema should call their physician immediately, as described in PL Sections 2 and 4. • Legal status: medicinal product subject to restricted medical prescription **Additional risk minimization measures:** • Healthcare professional checklist • Patient/caregiver guide	

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Bronchoconstriction	**Routine risk minimization 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 minimization 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 • PCSNSP003693 Survey to Assess the Effectiveness of Ponvory Educational Materials for Additional Risk Minimization Measures in the European Union Final report: December 2025 (1 year after the end of data collection)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Convulsions	**Routine risk minimization 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 minimization 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 • PCSNSP003693 Survey to Assess the Effectiveness of Ponvory Educational Materials for Additional Risk Minimization Measures in the European Union Final report: December 2025 (1 year after the end of data collection)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Potential Risks		
Severe liver injury	**Routine risk minimization 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 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 minimization 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 • PCSNSP003693 Survey to Assess the Effectiveness of Ponvory Educational Materials for Additional Risk Minimization Measures in the European Union Final report: December 2025 (1 year after the end of data collection)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Serious opportunistic infections including PML	**Routine risk minimization 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. • 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.	**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 • PCSNSP003693 Survey to Assess the Effectiveness of Ponvory Educational Materials for Additional Risk Minimization Measures in the European Union Final report: December 2025 (1 year after the end of data collection)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	• 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.	

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	• 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. • 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 immunization 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.	

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	• 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 minimization measures:** • Healthcare professional checklist • Patient/caregiver guide	
Skin cancer	**Routine risk minimization 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	**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 • PCSNSP003693 Survey to Assess the Effectiveness of Ponvory Educational Materials for Additional Risk Minimization Measures in the European Union Final report: December 2025 (1 year after the end of data collection)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	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 minimization measures:** • Healthcare professional checklist • Patient/caregiver guide	
Non-skin malignancy	**Routine risk minimization 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	**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 Minimization Measures	Pharmacovigilance Activities
	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 minimization measures:** • None	
Reproductive and embryofetal toxicity	**Routine risk minimization 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.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • PCSNSP004001: Ponesimod Pregnancy Outcomes Program Utilizing Enhanced Pharmacovigilance Monitoring (POEM) Final report: 19 May 2032 • PCSNSP003693 Survey to Assess the Effectiveness of Ponvory Educational Materials for Additional Risk Minimization Measures in the European Union Final report: December 2025 (1 year after the end of data collection)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	• 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. • 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	

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	Additional risk minimization measures: • Healthcare professional checklist • Patient/caregiver guide • Pregnancy-specific patient reminder card	
Unexpected neurological or psychiatric symptoms/signs (PRES, ADEM, atypical MS relapses)	**Routine risk minimization 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. • Legal status: medicinal product subject to restricted medical prescription **Additional risk minimization 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 **Additional pharmacovigilance activities:** • Trial AC-058B303/ OPTIMUM-LT Final report: 15/02/2025 • Trial AC-058B202 Final report: 14/12/2024 • PCSNSP003693 Survey to Assess the Effectiveness of Ponvory Educational Materials for Additional Risk Minimization Measures in the European Union Final report: December 2025 (1 year after the end of data collection)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Missing Information		
Use in elderly patients	**Routine risk minimization measures:** • SmPC Section 4.2 • Legal status: medicinal product subject to restricted medical prescription **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Cumulative reviews of reports of ponesimod use in elderly patients in the PBRER. **Additional pharmacovigilance activities:** • None
Long-term safety of ponesimod	**Routine risk minimization measures:** • Legal status: medicinal product subject to restricted medical prescription **Additional risk minimization 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

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for Ponvory (ponesimod)

This is a summary of the Risk Management Plan (RMP) for Ponvory. The RMP details important risks of Ponvory, how these risks can be minimized, and how more information will be obtained about Ponvory's risks and uncertainties (missing information).

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

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

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

I. The Medicine and What it is Used For

Ponvory is authorized for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features (see SmPC for the full indication). It contains ponesimod as the active substance and it is given by oral administration as 20-mg film-coated tablets after treatment initiation with a 14-day up-titration regimen, which includes 2-mg, 3-mg, 4-mg, 5-mg, 6-mg, 7-mg, 8-mg, 9-mg, and 10-mg film-coated tablets.

Further information about the evaluation of Ponvory's benefits can be found in Ponvory's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage link to the EPAR summary landing page.

II. Risks Associated With the Medicine and Activities to Minimize or Further Characterize the Risks

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

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

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and HCPs;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of Ponvory, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including Periodic Benefit-Risk Evaluation Report (PBRER) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

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

II.A. List of Important Risks and Missing Information

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

List of Important Risks and Missing Information	
Important identified risks	Bradyarrhythmia occurring post-first dose Macular edema Bronchoconstriction Convulsions
Important potential risks	Severe liver injury Serious opportunistic infections including PML Skin cancer Non-skin malignancy Reproductive and embryofetal toxicity Unexpected neurological or psychiatric symptoms/signs (PRES, ADEM, atypical MS relapses)
Missing information	Use in elderly patients Long-term safety of ponesimod

II.B. Summary of Important Risks

Important Identified Risk: Bradyarrhythmia occurring post-first dose	
Evidence for linking the risk to the medicine	In guinea pigs, single doses of ponesimod ≥0.3 mg/kg/day induced atrioventricular (AV) blocks and decreased heart rate (HR). These cardiovascular effects were significantly reduced on repeat dosing and after a low starting dose and up-titration (desensitization). Transient HR reductions and, less frequently, transient first- or second-degree AV block have been observed in the first days of treatment with ponesimod during the clinical development program. Bradycardia was identified as an adverse reaction. These findings and this adverse reaction are described in the SmPC.
Risk factors and risk groups	Risk factors include cardiac rhythm disorders or electrocardiogram (ECG) abnormalities indicative of an increased risk for arrhythmia, low resting HR, history of fainting or collapse, significant QT prolongation (ie, QT corrected [QTc] >500 ms), and concurrent therapy with anti-arrhythmic medicinal products, QT prolonging medicinal products, or medicinal products that slow HR. Patients with pre-existing cardiovascular comorbidities (such as ischemic heart disease, cardiac failure and history of cardiac arrest or myocardial infarction, cerebrovascular disease, uncontrolled hypertension, and presence of AV block) are also at increased risk.
Risk minimization measures	Routine risk minimization 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.

Important Identified Risk: Bradyarrhythmia occurring post-first dose	
	• 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. • 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 minimization measures: • Healthcare professional checklist • Patient/caregiver guide
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Trial AC-058B303/OPTIMUM-LT • PCSNSP003693: Survey to Assess the Effectiveness of Ponvory Educational Materials for Additional Risk Minimization Measures in the European Union See section II.C of this summary for an overview of the postauthorization development plan.

Important Identified Risk: Macular edema	
Evidence for linking the risk to the medicine	Cases of macular edema associated with changes in visual acuity have been reported in subjects treated with ponesimod during the clinical development program and macular edema was identified as an adverse reaction. This adverse reaction is described in the SmPC.
Risk factors and risk groups	Patients with a history of uveitis and patients with diabetes mellitus are at increased risk of developing macular edema during therapy with sphingosine-1-phosphate (S1P) receptor modulators.
Risk minimization measures	Routine risk minimization 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 edema until resolution, and patients with visual symptoms of macular edema 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 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 edema should call their physician immediately, as described in PL Sections 2 and 4. • Legal status: medicinal product subject to restricted medical prescription Additional risk minimization measures: • Healthcare professional checklist • Patient/caregiver guide
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • PCSNSP003693: Survey to Assess the Effectiveness of Ponvory Educational Materials for Additional Risk Minimization Measures in the European Union See section II.C of this summary for an overview of the postauthorization development plan.

Important Identified Risk: Bronchoconstriction	
Evidence for linking the risk to the medicine	In rats, a dose- and time-dependent effect on respiratory function was seen. The functional effect was characterized by a decrease in the relaxation time with a slight increase in the peak expiratory flow and tidal volume (increase in Penh), which indicates a transition from passive to more active expiration. Adverse events suggestive of bronchoconstriction and changes in pulmonary function in the form of a decrease in forced expiratory volume in 1 second (FEV_1) have been reported in subjects treated with ponesimod during the clinical development program. Dyspnea and cough were identified as adverse reactions. These findings and adverse reactions are described in the SmPC.
Risk factors and risk groups	No specific risk factors for bronchoconstriction have been identified.
Risk minimization measures	Routine risk minimization 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 minimization measures: • Healthcare professional checklist • Patient/caregiver guide
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Trial AC-058B303/OPTIMUM-LT • Trial AC-058B202 • PCSNSP003693: Survey to Assess the Effectiveness of Ponvory Educational Materials for Additional Risk Minimization Measures in the European Union See section II.C of this summary for an overview of the postauthorization development plan.

Important Identified Risk: Convulsions	
Evidence for linking the risk to the medicine	Cases of convulsions have been reported in subjects treated with ponesimod during the clinical development program and are described in the SmPC. Cases of seizure have been received from postmarketing sources. Seizures has been identified as an adverse drug reaction for other products in the same class. Although there is insufficient evidence to determine a causal relationship between convulsions/seizures and ponesimod treatment, a causal relationship is considered at least a reasonable possibility.
Risk factors and risk groups	No clear predisposing factors for convulsions could be identified.
Risk minimization measures	Routine risk minimization 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 minimization measures: • Healthcare professional checklist • Patient/caregiver guide
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Trial AC-058B303/OPTIMUM-LT • Trial AC-058B202 • PCSNSP003693: Survey to Assess the Effectiveness of Ponvory Educational Materials for Additional Risk Minimization Measures in the European Union See section II.C of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Severe liver injury	
Evidence for linking the risk to the medicine	As seen with other S1P receptor modulators, liver enzyme elevations, such as increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST), have been reported in subjects treated with ponesimod during the clinical development program and were identified as adverse reactions. These adverse reactions are described in the SmPC. Overall, the majority of ALT and AST elevations occurred within 6 or 12 months after ponesimod treatment initiation. There were no Hy's law cases in the ponesimod clinical program. Most cases of ALT increases ≥3x upper limit of normal were single transient asymptomatic episodes and resolved on continued ponesimod treatment; the rest resolved upon study treatment discontinuation.
Risk factors and risk groups	No specific risk factors for severe liver injury have been identified.
Risk minimization measures	Routine risk minimization 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 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 minimization measures: • Healthcare professional checklist • Patient/caregiver guide

Important Potential Risk: Severe liver injury	
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Trial AC-058B303/OPTIMUM-LT • Trial AC-058B202 • PCSNSP003693: Survey to Assess the Effectiveness of Ponvory Educational Materials for Additional Risk Minimization Measures in the European Union See section II.C of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Serious opportunistic infections including PML	
Evidence for linking the risk to the medicine	Cases of infections have been reported in subjects treated with ponesimod during the clinical development program. Several types of infection were identified as adverse reactions. These findings and adverse reactions are described in the SmPC. No cases of fatal infections have been reported in subjects treated with ponesimod during the clinical development program; however, life-threatening and rare fatal infections have been reported in association with other S1P receptor modulators.
Risk factors and risk groups	Patients in an immunodeficient state and those with severe active infections or active chronic infections are at increased risk for developing serious opportunistic infections including progressive multifocal leukoencephalopathy (PML).
Risk minimization measures	Routine risk minimization 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) complete blood count (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. • 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.

Important Potential Risk: Serious opportunistic infections including PML	
	• 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 cryptococcal meningitis (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 magnetic resonance imaging 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 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.

Important Potential Risk: Serious opportunistic infections including PML	
	• The use of live, attenuated vaccines should be avoided while on ponesimod therapy and up to 1 week after treatment discontinuation. If immunization 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 minimization measures: • Healthcare professional checklist • Patient/caregiver guide
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Trial AC-058B303/OPTIMUM-LT • Trial AC-058B202 • PCSNSP003693: Survey to Assess the Effectiveness of Ponvory Educational Materials for Additional Risk Minimization Measures in the European Union See section II.C of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Skin cancer	
Evidence for linking the risk to the medicine	Cases of skin cancer, including basal cell carcinoma and a case of malignant melanoma, have been reported in subjects treated with ponesimod during the clinical development program and are described in the SmPC. An increased risk of cutaneous malignancies has been reported in association with another S1P receptor modulator.
Risk factors and risk groups	Patients in an immunodeficient state and patients with a history of malignancies have an increased risk of developing skin cancer. There is also well-established scientific support for an association between ultraviolet radiation and skin cancer; sunlight can also cause immunosuppression.

Important Potential Risk: Skin cancer	
Risk minimization measures	Routine risk minimization 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 minimization measures: • Healthcare professional checklist • Patient/caregiver guide
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Trial AC-058B303/OPTIMUM-LT • Trial AC-058B202 • PCSNSP003693: Survey to Assess the Effectiveness of Ponvory Educational Materials for Additional Risk Minimization Measures in the European Union See section II.C of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Non-skin malignancy	
Evidence for linking the risk to the medicine	Rare cases of non-skin malignant neoplasms (including solid tumors and hematologic tumors) have been reported in subjects treated with ponesimod during the clinical development program.
Risk factors and risk groups	Patients in an immunodeficient state and patients with a history of malignancies have an increased risk of developing non-skin malignancy.
Risk minimization measures	Routine risk minimization 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, 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 minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Trial AC-058B303/OPTIMUM-LT • Trial AC-058B202 See section II.C of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Reproductive and embryofetal toxicity	
Evidence for linking the risk to the medicine	Reproductive and developmental studies in pregnant rats and rabbits have demonstrated ponesimod-induced developmental toxicity, including an increase in malformations (skeletal and visceral) and embryolethality. The area under the concentration-time curve from time 0 to 24 hours (AUC_{0-24}) in rats and rabbits at the no-observed-adverse-effect level (1 mg/kg/day in both species) are lower than the human systemic exposures at the recommended human dose of 20 mg/day. Ponesimod has not been studied in pregnant women. Clinical trials of ponesimod excluded pregnant and breast-feeding women. Clear recommendations how to avoid pregnancies in women of childbearing potential are described in the SmPC. Based on human experience in patients receiving another S1P receptor modulator, postmarketing data suggest that its use is associated with an increased risk of major congenital malformations.
Risk factors and risk groups	Women of childbearing potential who do not use effective contraception are at risk.
Risk minimization measures	Routine risk minimization 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.

Important Potential Risk: Reproductive and embryofetal toxicity	
	• 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 minimization measures: • Healthcare professional checklist • Patient/caregiver guide • Pregnancy-specific patient reminder card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • PCSNSP004001: Ponesimod Pregnancy Outcomes Program Utilizing Enhanced Pharmacovigilance Monitoring (POEM) • PCSNSP003693: Survey to Assess the Effectiveness of Ponvory Educational Materials for Additional Risk Minimization Measures in the European Union See section II.C of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Unexpected neurological or psychiatric symptoms/signs (PRES, ADEM, atypical MS relapses)	
Evidence for linking the risk to the medicine	No cases of posterior reversible encephalopathy syndrome (PRES) or acute disseminated encephalomyelitis (ADEM) have been reported in subjects treated with ponesimod during the clinical development program. However, rare cases of PRES have been reported in patients receiving other S1P receptor modulators. In clinical trials of another S1P receptor modulator, rare events involving the nervous system, including ischemic and hemorrhagic strokes and neurological atypical disorders such as ADEM-like events, occurred in patients treated at higher doses.
Risk factors and risk groups	Many patients with PRES have potentially severe comorbidities such as bone marrow or solid organ transplantation, chronic renal failure, and chronic hypertension, which may be predisposing factors. Infections and autoimmune disease have also been associated with PRES. Hypertension of renal origin has been reported to be a significant cause of PRES, and patients with renal dysfunction appear to be at higher risk of developing PRES.
Risk minimization measures	Routine risk minimization 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

Important Potential Risk: Unexpected neurological or psychiatric symptoms/signs (PRES, ADEM, atypical MS relapses)	
	neurological deterioration, and magnetic resonance imaging 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. • Legal status: medicinal product subject to restricted medical prescription Additional risk minimization measures: • Healthcare professional checklist • Patient/caregiver guide
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Trial AC-058B303/OPTIMUM-LT • Trial AC-058B202 • PCSNSP003693: Survey to Assess the Effectiveness of Ponvory Educational Materials for Additional Risk Minimization Measures in the European Union See section II.C of this summary for an overview of the postauthorization development plan.

Missing Information: Use in elderly patients	
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.2 • Legal status: medicinal product subject to restricted medical prescription Additional risk minimization measures: • None

Missing Information: Long-term safety of ponesimod	
Risk minimization measures	Routine risk minimization measures: • Legal status: medicinal product subject to restricted medical prescription Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Trial AC-058B303/OPTIMUM-LT • Trial AC-058B202 See section II.C of this summary for an overview of the postauthorization development plan.

II.C. Postauthorization Development Plan

II.C.1. Studies Which are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Ponvory.

II.C.2. Other Studies in Postauthorization Development Plan

PCSNSP004001: Ponesimod Pregnancy Outcomes Program Utilizing Enhanced Pharmacovigilance Monitoring (POEM).

Purpose of the study: To evaluate the potential risk of reproductive and embryofetal toxicity in pregnant women exposed to ponesimod.

The objective of this study is 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.

AC-058B303/OPTIMUM-LT - Multicenter, 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.

Purpose of the study: To characterize the long-term safety of ponesimod and control of disease in subjects with RMS and to investigate the effect on disease activity in a relatively large population after a brief interruption.

The objectives of this trial are 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.

AC-058B202 - Multicenter, randomized, 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.

Purpose of the study: To investigate the long-term safety, tolerability, and efficacy of ponesimod.

The objective of this trial is to investigate the long-term safety and tolerability of ponesimod.

PCSNSP003693: **Survey to Assess the Effectiveness of Ponvory Educational Materials for Additional Risk Minimization Measures in the European Union**

Purpose of the study: To assess the effectiveness of HCP and patient/caregiver educational materials (ie, healthcare professional checklist, patient/caregiver guide, and pregnancy-specific patient reminder card) aimed at minimizing important risks.

The objective of the survey of HCPs and patients/caregivers is to determine the effectiveness of the educational materials related to the understanding and management of Ponvory important identified and potential risks in the European Union.

PART VII: ANNEXES

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Annex 4: Specific Adverse Drug Reaction Follow-up Forms

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Healthcare professional adverse event follow-up form[4]

Ponesimod Convulsions Follow-up questionnaire.

Ponesimod Serious opportunistic infections including PML Follow-up questionnaire.

Ponesimod Unexpected neurological or psychiatric symptoms/signs (PRES, ADEM, Atypical MS relapses) Follow-up questionnaire.

[4] The healthcare professional adverse event follow-up form or local approved form is sent to the reporter along with the targeted follow-up questionnaires.

HEALTH CARE PROFESSIONAL ADVERSE EVENT FOLLOW-UP FORM

Return in postage-paid envelope enclosed, or fax to +1 215-293-9955

Product:	AER No.:	Other ID No.:

Patient

Patient Name (Print):

Height:	Weight:	Gender:	Age:	Date of Birth:	Age Group (if age or DOB is not available)
					☐ Birth – 28 days ☐ 29 days – 24 months ☐ 24 months – 13 years ☐ 14 years – 18 years ☐ 19 years – 65 years ☐ Over 65 years

	PRIMARY Suspect Medication	OTHER Suspect Medication		
		#1	#2	#3
Generic name				
Trade/brand name				
Biosimilar?	Y ☐ N ☐ Unknown ☐ N/A ☐	Y ☐ N ☐ Unk ☐ N/A ☐	Y ☐ N ☐ Unk ☐ N/A ☐	Y ☐ N ☐ Unk ☐ N/A ☐
Indication				
Dose/unit/frequency				
Approximate total number of doses/ injections/infusions patient received				
Route/formulation				
Therapy dates (start and stop)				
Lot #				
Expiration date				

Does the patient have allergies?	☐ No ☐ Yes – details:
Was the patient pregnant?	☐ No ☐ Yes – last menstrual period date:
Does the patient drink alcohol?	☐ No ☐ Yes – units per week:
Does the patient smoke?	☐ No ☐ Yes – how much per day:
Is there a history of drug abuse?	☐ No ☐ Yes – details:

Device/Combo Product Device

Is the complaint related to a specific part used to administer the product?	No ☐ Yes ☐ **If Yes, document the specific details about how the issue occurred (complete questions below by checking the boxes):**	Describe which specific part of the Device or device component was involved:
When did the problem occur?	Before use/in package ☐ During preparation ☐ During use/administration ☐ After use/during disposal ☐ Unknown ☐	
Did the patient experience harm from the product problem?	No ☐ Yes ☐ Unk ☐ Describe:	
Were the product instructions for use followed?	No ☐ Yes ☐ Unk ☐ If not, explain why:	Number of units involved?
Who was using the Device (Operator of device)?	Health Professional ☐ Lay User/Patient ☐ Other ☐ If Other, describe:	Single use device was reprocessed and reused? No ☐ Yes ☐
Usage of Device	Initial Use ☐ Reuse ☐ Unk ☐	

Reporter

Reporter's Name:

☐ Nurse ☐ Physician - Specialty: ☐ Pharmacist ☐ Other - Specify:

Address:

Telephone: Fax:

Product: AER No.: Other ID No.:

Concomitant Therapy: Other medication (including botanical remedies and nutraceuticals) received no longer than 2 weeks prior to event				
Name	Indication	Dates of therapy	Dose	Lot #

Provide the underlying clinical diagnosis – if unknown, list as relevant signs and symptoms			
	Adverse Event #1	Adverse Event #2	Adverse Event #3
Adverse Event Diagnosis			
Seriousness	☐ Non-serious ☐ Serious - Specify: ☐ Event directly led to death ☐ Event was an immediate threat to life ☐ Hospitalization ☐ Persistent/significant disability ☐ Congenital anomaly/birth defect ☐ Other medically important condition	☐ Non-serious ☐ Serious - Specify: ☐ Event directly led to death ☐ Event was an immediate threat to life ☐ Hospitalization ☐ Persistent/significant disability ☐ Congenital anomaly/birth defect ☐ Other medically important condition	☐ Non-serious ☐ Serious - Specify: ☐ Event directly led to death ☐ Event was an immediate threat to life ☐ Hospitalization ☐ Persistent/significant disability ☐ Congenital anomaly/birth defect ☐ Other medically important condition
Onset Date			
Primary Suspect Medication	Causality: ☐ Not related ☐ Related Action taken with drug: ☐ Drug withdrawn ☐ Drug interrupted ☐ Dose reduced ☐ Dose increased ☐ Dose not changed ☐ Unknown ☐ Not applicable	Causality: ☐ Not related ☐ Related Action taken with drug: ☐ Drug withdrawn ☐ Drug interrupted ☐ Dose reduced ☐ Dose increased ☐ Dose not changed ☐ Unknown ☐ Not applicable	Causality: ☐ Not related ☐ Related Action taken with drug: ☐ Drug withdrawn ☐ Drug interrupted ☐ Dose reduced ☐ Dose increased ☐ Dose not changed ☐ Unknown ☐ Not applicable
	Recent dose change? (Elaborate on timing/amount of dose change): Did the reaction abate after the drug was withdrawn, interrupted, or reduced? ☐ Yes ☐ No If drug reintroduced, did reaction recur? ☐ Yes ☐ No	Recent dose change? (Elaborate on timing/amount of dose change): Did the reaction abate after the drug was withdrawn, interrupted, or reduced? ☐ Yes ☐ No If drug reintroduced, did reaction recur? ☐ Yes ☐ No	Recent dose change? (Elaborate on timing/amount of dose change): Did the reaction abate after the drug was withdrawn, interrupted, or reduced? ☐ Yes ☐ No If drug reintroduced, did reaction recur? ☐ Yes ☐ No

Product: AER No.: Other ID No.:

Provide the underlying clinical diagnosis – if unknown, list as relevant signs and symptoms			
	Adverse Event #1	Adverse Event #2	Adverse Event #3
Outcome	☐ Recovered without sequelae ☐ Recovered with sequelae Recovery date: ☐ Recovering ☐ Not recovered ☐ Fatal (event directly led to death) ☐ Unknown	☐ Recovered without sequelae ☐ Recovered with sequelae Recovery date: ☐ Recovering ☐ Not recovered ☐ Fatal (event directly led to death) ☐ Unknown	☐ Recovered without sequelae ☐ Recovered with sequelae Recovery date: ☐ Recovering ☐ Not recovered ☐ Fatal (event directly led to death) ☐ Unknown
If Applicable	Hospital admission date: Patient had emergency department visit and discharged? ☐ Yes ☐ No	Hospital discharge date:	
	Date of death:	Was an autopsy performed? ☐ No ☐ Yes (attach copy of report if available)	

Adverse Event Description	Describe the course of events including timing with respect to drug administration (use additional pages if necessary)
Relevant medical history and family history	
Signs & Symptoms	
Course of Event	
Relevant results of diagnostic tests (imaging, laboratory tests, biopsies, etc.)	
Diagnosis	
Treatment & response	
Suspected causes/risk factors	

Ponesimod Targeted Follow-Up Questionnaire (TFUQ) for Convulsions

Manufacturer Control Number: Date of Report: [dd-MMM-yyyy]

In addition to collecting routine information for this adverse event, ensure the following additional information is provided and/or confirmed.

1. Relevant medical history

Specify medical condition, if it is concurrent or pre-existing, and date of onset.

- ☐ Genetic disease or familial predisposition:
- ☐ Congenital brain defects:
- ☐ Peri or postpartum brain injury:
- ☐ Idiopathic seizures:
- ☐ Brain tumor or other structural brain lesion (e.g., bleeding):
- ☐ Infections (brain abscess, meningitis, encephalitis, neurosyphilis, AIDS):
- ☐ Dementia (e.g., Alzheimer's disease):
- ☐ Traumatic brain injury, stroke, or a transient ischemic attack:
- ☐ Migraines with focal symptoms or aura:
- ☐ Phenylketonuria (PKU):
- ☐ Kidney or liver failure:
- ☐ Sleep disorders:
- ☐ Menstrual cycle (specify, e.g., day 1, ovulation, second half cycle):
- ☐ Illness resulting in brain deterioration:
- ☐ Stopping alcohol after drinking heavily on most days:
- ☐ Use of barbiturates/benzodiazepines:
- ☐ Drugs of abuse (e.g., cocaine):
- ☐ Psychiatric disorders:
- ☐ Emotional stress:
- ☐ Hyperventilation:
- ☐ Other, specify:
- ☐ None

Was the patient taking any of the following drugs at the time of the event? Check all that apply.

- ☐ Antibiotics (e.g., penicillin, ampicillin, carbenicillin, cephalosporin)
- ☐ Antidepressants (e.g., bupropion, tricyclics)
- ☐ Analgesics (e.g., Fentanyl, mefenamic acid, tramadol, meperidine)
- ☐ Antipsychotic medications (e.g., chlorpromazine, haloperidol, clozapine, atypicals)
- ☐ Antineoplastic agents (e.g., busulfan, carmustine, chlorambucil, methotrexate)
- ☐ Phenothiazines
- ☐ Metoclopramide
- ☐ Drugs of abuse
- ☐ Bronchial agents (e.g., aminophylline, theophylline)
- ☐ Lithium
- ☐ Sympathomimetics (e.g., ephedrine, phenylpropanolamine, terbutaline)
- ☐ General/local anesthetics (e.g., enflurane, ketamine, methohexital, bupivacaine, lidocaine, procaine)
- ☐ OTC and/or natural remedies, specify:
- ☐ Immunosuppressants (steroids, cyclosporine)
- ☐ Anticonvulsants
- ☐ None of the above

Did the patient have a prior history of seizure? If yes, provide classification and description:

MCN:

2. **Event precipitant or trigger. Was the patient exposed to or experienced any of the following around the time of or immediately prior to the seizure?** Check all that apply and describe:

☐ Stress, excitement, emotional upset	☐ Alcohol
☐ Loud music	☐ Fever
☐ Missed anti-epileptic medication	☐ Acute or exacerbation of chronic infection/exacerbation of systemic illness, specify:
☐ Menstruation	☐ Metabolic dysbalance (e.g., hypoglycemia, hyponatremia, hypocalcemia, vitamin D deficiency), specify:
☐ Intense exercise	☐ Lack of sleep
☐ Flashing lights	☐ None

3. **Event description. Did the patient present with any of the following signs/symptoms?** Check all that apply and describe:

Aura

☐ Visual disturbance	☐ Fear/panic
☐ Headache	☐ Nausea/abdominal sensation
☐ Depression/irritability/sleep disruption	☐ Dizziness/lightheadedness
☐ Deja vu/jamais vu/smell/sound/taste	☐ No Aura

☐ Changes in bodily sensations, ability to interact, unfamiliarity with outside world

Postictal

☐ Memory loss ☐ Confusion ☐ Weakness ☐ Somnolence ☐ Lethargy

4. **Classification of current seizure.** Check all that apply.

Generalized seizures

Seizure classification	Symptoms
☐ "Grand Mal" or Generalized tonic-clonic	☐ Unconsciousness, convulsions, muscle rigidity
☐ Absence	☐ Brief loss of consciousness
☐ Myoclonic	☐ Sporadic (isolated), jerking movements
☐ Clonic	☐ Repetitive, jerking movements
☐ Tonic	☐ Muscle stiffness, rigidity
☐ Atonic	☐ Loss of muscle tone

Focal seizures

Seizure classification	Symptoms
☐ Aura (formerly simple somatosensory)	☐ Jerking, muscle rigidity, spasms, head-turning
☐ Motor	☐ Unusual sensations affecting either the vision, hearing, smell taste or touch
☐ Autonomic	☐ Memory or emotional disturbances
☐ Clonic	☐ Dyscognitive (formerly complex) Automatisms such as lip smacking, chewing, fidgeting, walking and other repetitive, involuntary but coordinated movements
☐ Focal seizure secondarily generalized	☐ Symptoms initially associated with a preservation of consciousness that evolves into a loss of consciousness and convulsions

MCN:

5. Were the seizures witnessed?
☐ Unknown ☐ No ☐ Yes (describe, include type and duration):

6. Were any of the following diagnostic tests performed? Check all that apply and specify which test(s), dates, and results:
☐ Neurological investigations (e.g., EEG, CT scan, MRI scan, PET, SPECT, video-EEG, lumbar puncture):
☐ General investigations (e.g., CBC, blood chemistry, urinalysis, alcohol screen, toxic screen):

☐ Other (specify):
☐ None of the above

Ponesimod Targeted Follow-Up Questionnaire (TFUQ) for Serious Opportunistic Infections including PML

Manufacturer Control Number: Date of Report: [dd-MMM-yyyy]

In addition to collecting routine information for this adverse event, ensure the following additional information is provided and/or confirmed.

This checklist has 2 parts: Part 1 should be completed always. Part 2 should be completed in case of suspected PML.

PART 1. To be completed

1. Patient history

Does the patient have a history of any of the following prior to the start of Ponesimod (PONVORY®)? Check all that apply and include date(s) of onset as well as status (i.e., active/inactive) and details.

- ☐ Chronic disease (e.g., diabetes):
- ☐ Recurrent infections or chronic infections:
- ☐ Trauma with open wound or burns:
- ☐ Long-term use of antibiotics:
- ☐ Corticosteroid use:
- ☐ Malignancy (e.g., Leukemia, Lymphoma, Myeloproliferative disease):
- ☐ Weakened immune system (e.g., HIV/AIDS):
- ☐ Other disturbances of the immune system (e.g., history of low CD4/CD8 ratio):
- ☐ Other relevant history, specify:
- ☐ Poor nutritional status (e.g., BMI < 21):
- ☐ Sarcoidosis:
- ☐ Invasive device (e.g., dialysis, catheter, feeding tube):
- ☐ Surgical procedure:
- ☐ Recent travel to endemic disease areas or contact with contagious agent:
- ☐ Close contact with birds:
- ☐ Contact with eucalyptus trees:
- ☐ Poor social status:
- ☐ None of the above

How long has the patient had Multiple Sclerosis? (years/months or specific date of diagnosis):

List all MS treatments and duration:

Drug	Dose	Start and stop dates of therapy

List all concomitant or recent (i.e. within the past 6 months) immunosuppressive therapies. Check all that apply and include dates of starting and completing the medication, and dose.

- ☐ Monoclonal antibodies (e.g., natalizumab, efalizumab, infliximab, rituximab), specify:
- ☐ Steroids:
- ☐ Radiation therapy:
- ☐ Chemotherapy/Cytoreductive therapy, specify:
- ☐ Other immunosuppressant drugs, specify:
- ☐ None of the above

MCN:

2. Event description. Summary of clinical course

Approximate onset date of symptoms that led to the diagnosis:
What were the initial presenting symptoms/signs?:

3. Was there infection of the central nervous system?

☐ Yes ☐ No ☐ Unknown

If yes, did the patient present with any of the following signs or symptoms? Check all that apply:

☐ Hemiparesis	☐ Cognitive impairment	☐ Weakness
☐ Hemianopia	☐ Personality changes	☐ Fever
☐ Brainstem deficits	☐ Dysarthria	☐ Headaches
☐ Clumsiness/Cerebellar deficits	☐ Aphasia	☐ Others, specify:
☐ Sensory deficits	☐ Visual impairment	☐ None of the above

4. Diagnostic tests. Check all that apply and specify reference range if applicable.

Test	Baseline levels (at Ponesimod [PONVORY®] start)				Current levels (at onset of infection)			
	Date	Result (Ref. range)	Unit		Date	Result (Ref. range)	Unit	
Absolute neutrophil count				☐ Unknown				☐ Unknown
Absolute lymphocyte count				☐ Unknown				☐ Unknown
Absolute white blood count				☐ Unknown				☐ Unknown

5. Were any of the following diagnostic tests performed? Check all that apply and describe.

☐ Culture of blood, urine, cerebrospinal, peritoneal or pleural fluids
☐ Imaging studies (e.g. MRI, CAT or CT)
☐ Bone marrow examination
☐ Specialized serologic tests
☐ None of the above

Results:

6. Treatment. Specify the treatment received.

Did the patient receive intravenous treatment for infection?
☐ Yes ☐ No ☐ Unknown

Did the clinical course of infection require change of treatment for infection?
☐ Yes ☐ No ☐ Unknown

Did the treatment for infection require strength and/or frequency change?
☐ Yes ☐ No ☐ Unknown

MCN:

7. Diagnosis. Include corresponding event onset dates.

Is the event a newly identified/ new onset infection?
☐ Yes ☐ No ☐ Unknown
Is the infection an exacerbation of previous infection?
☐ Yes ☐ No ☐ Unknown
Is the infection chronic?
☐ Yes ☐ No ☐ Unknown
Is the infection considered to be "opportunistic"?
☐ Yes ☐ No ☐ Unknown

Agent/microorganism

Is the infection caused by a Gram-positive bacterium?
☐ Yes ☐ No ☐ Unknown
Is the infection caused by a Gram-negative bacterium?
☐ Yes ☐ No ☐ Unknown

Is the infection:

Mycobacterial infection?
☐ Yes ☐ No ☐ Unknown
Pseudomonas aeruginosa infection?
☐ Yes ☐ No ☐ Unknown
Polyomavirus infection? **If yes, fill out Part 2**
☐ Yes ☐ No ☐ Unknown
Cytomegalovirus infection?
☐ Yes ☐ No ☐ Unknown
Toxoplasma infection?
☐ Yes ☐ No ☐ Unknown
Systemic fungal infection (e.g., Cryptococcal, Aspergillus or Pneumocystis infection)?
☐ Yes ☐ No ☐ Unknown
Any other opportunistic infection?
☐ Yes ☐ No ☐ Unknown
If yes, specify:

MCN:

PART 2. To be completed in case of suspected PML

8. Work up for the event.

Was brain MRI/MRA performed?
☐ Yes, provide the report and confirm if MRI sent for external expert review
☐ No ☐ Unknown Results:

Was a Cerebrospinal Fluid (CSF) analysis performed?
☐ Yes ☐ No ☐ Unknown
If yes, which analyses were performed?

Polymerase Chain Reaction (PCR) testing done for JCF? Provide results and date of sample
☐ Yes ☐ No ☐ Unknown
If yes, state whether CSF has been sent for analysis at a central reference laboratory (e.g. at NIH):
Results:

Serology done for antibody to JC Virus (JCV)? Provide results and date of sample
☐ Yes ☐ No ☐ Unknown
Results:

Was a blood/urine analysis performed?
☐ Yes ☐ No ☐ Unknown
If yes, which analyses were performed?

Serology done for antibody to JC Virus (JCV)? Provide results and date of sample
☐ Yes ☐ No ☐ Unknown
Results:

Hematological parameters (WBC incl. differentials). Provide results and date of sample
☐ Yes ☐ No ☐ Unknown
Results:

Others. Provide results and date of sample.
☐ Yes ☐ No ☐ Unknown
Results:

Was an EEG performed?
☐ Yes, provide report ☐ No ☐ Unknown
Findings:

Was a brain CT scan performed?
☐ Yes, provide report ☐ No ☐ Unknown
Findings:

Was brain biopsy performed?
☐ Yes, provide report ☐ No ☐ Unknown
Findings:

Were any other tests performed?
☐ Yes, specify and provide report: ☐ No ☐ Unknown
Findings:

Ponesimod Targeted Follow-Up Questionnaire (TFUQ) for Unexpected Neurological or Psychiatric Symptoms/Signs (PRES, ADEM, Atypical MS Relapses)

Manufacturer Control Number: Date of Report: [dd-MMM-yyyy]

In addition to collecting routine information for this adverse event, ensure the following additional information is provided and/or confirmed.

1. Patient history

First MS symptoms (describe symptoms and dates):

Previous disease modifying treatment(s) before ponesimod (provide start and stop dates, circle last drug taken):

☐ Interferon beta-1a: ☐ Glatiramer acetate: ☐ Interferon beta-1b:
☐ Mitoxantrone: ☐ Natalizumab: ☐ Others (specify):
Treatment details:

2. Clinical and radiological disease activity

Prior to start of first disease modifying treatment for MS:
☐ **Expanded disease disability scale (EDSS) score:**
☐ MRI results:

Prior to start of ponesimod (PONVORY®)
☐ **Expanded disease disability scale (EDSS) score:**
☐ MRI results:

3. Signs and symptoms of the adverse event

Motor system
☐ Spasticity
☐ Paresis/plegia
☐ Others:

Sensory system
☐ Numbeness
☐ Headache
☐ Others:

Visual system
☐ Vision loss/blindness
☐ Reduced color vision
☐ Others:

Cognitive system
☐ Confusion
☐ Language impaired
☐ Memory loss
☐ Others:

Brainstem system
☐ Slurred speech
☐ Nystagmus
☐ Trouble swallowing

Cerebellar system
☐ Ataxia
☐ Poor coordination
☐ Slurred speech
☐ Coma

Bowel/bladder
☐ Incontinence
☐ Retention
☐ Impotence
☐ Others:

Others
☐ Seizure (date of onset and type of seizure:
☐ Meningismus
☐ Fever (date of onset):

Did the patient experience infection within the last 30 days?
☐ Yes, specify date of onset and type:
☐ No
☐ Unknown

MCN:

4. Expanded Disability Status Scale (EDSS) score during event onset:

5. Work up for the event

Imaging investigations (provide summary of results and copy of the results, including date):

MRI performed?	☐ Yes	☐ No	☐ Unknown
CT scan performed?	☐ Yes	☐ No	☐ Unknown

Others (specify):

Laboratory investigations (provide summary of results and copy of the results, including date and reference ranges):

Blood analysis performed?	☐ Yes	☐ No	☐ Unknown
CSF analysis performed?	☐ Yes	☐ No	☐ Unknown

Results (including onset date):
Others (specify):

EEG(s) performed? (provide summary of results and copy of the results, including date):

☐ Yes ☐ No ☐ Unknown

Results:

Brain biopsy performed? (provide summary of results and copy of the results, including date):

☐ Yes ☐ No ☐ Unknown

Results:

Additional investigations if available (provide summary of results and copy of the results, including date):

Annex 6: Details of Proposed Additional Risk Minimization Activities (if applicable)

Approved Key Messages of the Additional Risk Minimization Measures

Prior to the launch of Ponvory in each Member State, the Marketing Authorization Holder (MAH) must agree on the content and format of the educational program, including communication media, distribution modalities, and any other aspects of the program, with the National Competent Authority.

The MAH shall ensure that in each Member State where Ponvory is marketed, all healthcare professionals (HCPs) who intend to prescribe Ponvory are provided with a Healthcare Professional Information Pack, which contains the following:

- Information on where to find the latest Ponvory Summary of Product Characteristics (SmPC);
- Healthcare professional checklist;
- Patient/caregiver guide;
- Pregnancy-specific patient reminder card.

Healthcare professional checklist

The healthcare professional checklist shall contain the following key messages:

- Dose escalation at treatment initiation:
  - Start treatment on Day 1 with one 2-mg tablet orally once daily and progress with the 14-day titration schedule outlined in the following table:

Titration day	Daily dose
Days 1 and 2	2 mg
Days 3 and 4	3 mg
Days 5 and 6	4 mg
Day 7	5 mg
Day 8	6 mg
Day 9	7 mg
Day 10	8 mg
Day 11	9 mg
Days 12, 13, and 14	10 mg

  After dose titration is complete, the recommended maintenance dose of Ponvory is one 20-mg tablet taken orally once daily.
- Re-initiation of Ponvory therapy following treatment interruption during dose titration or maintenance period:
  - If fewer than 4 consecutive doses are missed, resume treatment with the first missed dose.
  - If 4 or more consecutive doses are missed, re-initiate treatment with Day 1 (2 mg) of the titration regimen (new treatment initiation pack).

  The same first-dose monitoring as for treatment initiation is recommended when 4 or more consecutive doses of Ponvory are missed during the titration or maintenance periods.

- Mandatory requirements before initiating treatment:

Before first dose of Ponvory

- Perform an electrocardiogram (ECG) to determine whether first-dose monitoring is needed. In patients with certain pre-existing conditions, first dose monitoring is recommended (see below).
- Review results of a complete blood count (CBC) with differential (including lymphocyte count) obtained within 6 months prior to treatment initiation or after discontinuation of prior therapy.
- Perform a liver function test (transaminases, bilirubin) within 6 months prior to treatment initiation.
- Obtain an evaluation of the fundus, including the macula, prior to treatment initiation. Ponvory therapy should not be initiated in patients with macular edema until resolution.
- A negative pregnancy test result must be available prior to treatment initiation in women of childbearing potential.
- Perform a varicella zoster virus (VZV) antibody test in patients without a HCP-confirmed history of varicella or without documentation of a full course of vaccination against VZV. If negative, VZV vaccination is recommended at least 4 weeks prior to treatment initiation with Ponvory to allow the full effect of vaccination to occur.
- Initiation of treatment with Ponvory should be delayed in patients with severe active infection until resolution.
- Review current or prior medications. If patients are taking anti-neoplastic, immunosuppressive, or immune-modulating therapies, or if there is a history of prior use of these medicinal products, consider possible unintended additive effects on the immune system before treatment initiation.
- Determine whether patients are taking medicinal products that could slow down heart rate (HR) or atrioventricular (AV) conduction.

First-dose monitoring

- Recommended for patients with sinus bradycardia (HR <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 who are in stable condition.
- Monitor patients for signs and symptoms of bradycardia for 4 hours after the first dose with a minimum of hourly pulse and blood pressure measurements.
- Obtain an ECG in these patients at the end of the 4-hour observation period.
- Extend the monitoring until resolution of findings if:
  - HR at 4 hours postdose is <45 bpm,
  - HR at 4 hours postdose is at the lowest value postdose, or
  - ECG at 4 hours postdose shows new onset second-degree or higher AV block.
- If pharmacological treatment is required, continue monitoring overnight and repeat 4-hour monitoring after the second dose.
- Cardiologist advice should be obtained before initiation of Ponvory in the following patients to determine overall benefit-risk and the most appropriate monitoring strategy:
  - Patients with significant QT prolongation (QTc >500 ms) or who are already being treated with QT-prolonging medicinal products with known arrhythmogenic properties (risk of torsades de pointes).
  - Patients with atrial flutter/fibrillation or arrhythmias treated with Class Ia (eg, quinidine, procainamide) or Class III (eg, amiodarone, sotalol) anti-arrhythmic medicinal products.

  - Patients with unstable ischemic heart disease, cardiac decompensated failure occurring more than 6 months prior to treatment initiation, history of cardiac arrest, cerebrovascular disease (TIA, stroke occurring more than 6 months prior to treatment initiation), and uncontrolled hypertension, since significant bradycardia may be poorly tolerated in these patients, treatment is not recommended.
  - Patients with a history of Mobitz Type II second-degree AV block or higher-grade AV block, sick-sinus syndrome, or sino-atrial heart block.
  - Patients with a history of recurrent syncope or symptomatic bradycardia.
  - Patients receiving concurrent therapy with drugs that decrease HR (eg, beta-blockers, nondihydropyridine calcium channel blockers [diltiazem and verapamil], and other drugs that may decrease HR, such as digoxin); consider the need to switch to non-HR-lowering medicinal products. Concomitant use of these medicinal products during Ponvory initiation may be associated with severe bradycardia and heart block.

- Ponvory is contraindicated in the following patients:
  - Patients who have hypersensitivity to the active substance or to any of the excipients.
  - Patients in an immunodeficient state.
  - Patients who have in the last 6 months experienced myocardial infarction, unstable angina, stroke, TIA, decompensated heart failure requiring hospitalization, or New York Heart Association (NYHA) Class III/IV heart failure.
  - Patients who have presence of Mobitz type II second-degree AV block, third-degree AV block, or sick-sinus syndrome, unless the patient has a functioning pacemaker.
  - Patients with severe active infections and patients with active chronic infections.
  - Patients with active malignancies.
  - Patients with moderate or severe hepatic impairment (Child Pugh class B and C, respectively).
  - Women who are pregnant and women of childbearing potential not using effective contraception.
- Ponvory reduces peripheral blood lymphocyte counts. Results of a CBC with differential (including lymphocyte count) obtained within 6 months prior to treatment initiation or after discontinuation of prior therapy should be reviewed in all patients prior to treatment initiation. Assessments of CBC are also recommended periodically during treatment. Absolute lymphocyte counts $<0.2x10^9$/L, if confirmed, should lead to interruption of Ponvory therapy until the level reaches $>0.8x10^9$/L, after which re-initiation of Ponvory can be considered.
- Ponvory has an immunosuppressive effect that predisposes patients to infections, including opportunistic infections that can be fatal, and may increase the risk of developing malignancies, particularly those of the skin. Patients should be carefully monitored, especially those with concurrent conditions or known risk factors, such as previous immunosuppressive therapy. Discontinuation of treatment in patients at increased risk of infections or malignancies should be considered on a case-by-case basis.
  - Delay initiation of treatment with Ponvory in patients with severe active infections until resolved. Suspension of treatment during serious infection should be considered. Anti-neoplastic, immune-modulating, or immunosuppressive therapies should be co-administered with caution due to the risk of additive immune system effects, also for patients with a history of prior use. For the same reason, a decision to use prolonged concomitant treatment with corticosteroids should be taken after careful consideration and the half-life and mode of action

of medicinal products with prolonged immune effects should be considered when switching from these medicinal products.

- Vigilance for skin malignancies is recommended. Caution patients against exposure to sunlight and UV light without protection. Patients should not receive concomitant phototherapy with ultraviolet B (UVB) radiation or psoralen and ultraviolet A (PUVA) photochemotherapy. Patients with pre-existing skin disorders and patients with new or changing skin lesions should be referred to a dermatologist to determine appropriate monitoring.

- Patients should be instructed to report signs and symptoms of infections immediately to their prescriber during treatment and for up to 1 week after the last dose of Ponvory. Physicians should also be vigilant for signs and symptoms of infection.
  - If cryptococcal meningitis (CM) is suspected, treatment with Ponvory should be suspended until cryptococcal infection has been excluded. If CM is diagnosed, appropriate treatment should be initiated.
  - Cases of fatal CM and disseminated cryptococcal infections have been reported in patients treated with other sphingosine-1-phosphate (S1P) receptor modulators.
  - Physicians should be vigilant for clinical signs and symptoms or magnetic resonance imaging (MRI) findings suggestive of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain caused by the John Cunningham polyoma virus. If PML is suspected, treatment with Ponvory should be suspended until PML has been excluded. If PML is confirmed, treatment with Ponvory should be discontinued.
  - Cases of PML have been reported in patients treated with another S1P receptor modulator and other multiple sclerosis (MS) therapies.
  - Use of live attenuated vaccines may carry a risk of infection and should therefore be avoided during treatment with Ponvory and up to 1 week after treatment discontinuation. If immunization with a live attenuated vaccine is required, Ponvory treatment should be paused from 1 week prior to 4 weeks after a planned vaccination.
- An ophthalmic evaluation of the fundus, including the macula, is recommended in all patients:
  - Prior to treatment initiation with Ponvory.
  - At any time if a patient reports any change in vision while on Ponvory therapy. Ponesimod therapy should not be initiated in patients with macular edema until resolution. Patients who present with visual symptoms of macular edema should be evaluated; if macular edema is confirmed, treatment with Ponvory should be discontinued. After resolution of macular edema, the potential benefits and risks of Ponvory should be considered before treatment re-initiation.
  - Patients with a history of uveitis or diabetes mellitus should have regular examinations of the fundus, including the macula, prior to treatment initiation with Ponvory, and have follow-up evaluations while receiving therapy.
- Ponvory is contraindicated during pregnancy and in women of childbearing potential not using effective contraception.
  - A negative pregnancy test result must be available in women of childbearing potential prior to treatment initiation; pregnancy testing must be repeated at suitable intervals during treatment.
  - Before initiation and during Ponvory treatment, women of childbearing potential should be counseled on the potential for a serious risk to the fetus during treatment with Ponvory, facilitated by the pregnancy-specific patient reminder card.
  - Women of childbearing potential must use effective contraception during treatment with Ponvory and for at least 1 week following treatment discontinuation.

  - Treatment with Ponvory must be discontinued at least 1 week before attempting to conceive.
  - Disease activity may return when treatment with Ponvory is discontinued due to pregnancy or attempting to conceive.
  - If a woman becomes pregnant during treatment, Ponvory must be immediately discontinued. Medical advice should be given regarding the risk of harmful effects to the fetus associated with Ponvory treatment and follow-up examinations should be performed.
  - Ponvory should not be used during breast-feeding.
  - Physicians are encouraged to enroll pregnant patients in the Ponesimod Pregnancy Outcomes Program Utilizing Enhanced Pharmacovigilence Monitoring (POEM), or pregnant women may enroll themselves.

- Elevation of transaminases and bilirubin may occur in patients taking Ponvory. Before treatment initiation, results of a liver function test obtained within the last 6 months should be reviewed. Patients who develop symptoms suggestive of hepatic dysfunction during treatment with Ponvory should be monitored for hepatotoxicity, and treatment should be discontinued if significant liver injury is confirmed (eg, alanine aminotransferase [ALT] exceeds 3x upper limit of normal (ULN) and total bilirubin exceeds 2xULN).
- Ponvory may cause a decline in pulmonary function. Spirometry evaluation of respiratory function during treatment with Ponvory should be performed if clinically indicated.
- Blood pressure should be regularly monitored during treatment with Ponvory.
- Seizures have been reported in patients treated with Ponvory. Physicians should be vigilant for seizures, especially in those patients with a pre-existing history of seizures or a family history of epilepsy.
- Rare cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients receiving an S1P receptor modulator. If a Ponvory-treated patient develops unexpected neurological or psychiatric signs or symptoms, signs or symptoms suggestive of increased intracranial pressure, or accelerated neurological deterioration, a complete physical and neurological examination should promptly be scheduled, and an MRI should be considered. Symptoms of PRES are usually reversible but may evolve into ischemic stroke or cerebral hemorrhage. Delay in diagnosis and treatment may lead to permanent neurological sequelae. If PRES is suspected, treatment with Ponvory should be discontinued.

Patient/caregiver guide

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

- What Ponvory is and how it works.
- What multiple sclerosis is.
- Patients should read the package leaflet thoroughly before starting treatment and should keep it in case they need to refer to it during treatment.
- Patients should have an ECG prior to receiving their first dose of Ponvory to determine whether first-dose monitoring is required. An ECG should also be done before treatment re-initiation when 4 or more consecutive doses are missed.
- When initiating treatment with Ponvory, patients should use a treatment initiation pack and should follow the 14-day titration schedule.

- Patients should immediately report any signs and symptoms indicative of slow HR (eg, dizziness, vertigo, nausea, and palpitations) after the first dose of Ponvory to their prescriber.
- Patients should contact their prescriber in case of treatment interruption (ie, 4 or more consecutive doses are missed). Patients should not restart treatment with Ponvory without seeking advice from their prescriber, as they may need to restart treatment with a new treatment initiation pack.
- Patients should have a recent (ie, within 6 months or after discontinuation of prior therapy) blood test of the blood cells prior to receiving their first dose of Ponvory.
- Patients who have not been infected with VZV (chickenpox) or who have not previously been vaccinated against VZV should be tested and if needed are recommended to be vaccinated at least 4 weeks prior to starting Ponvory treatment.
- Patients should immediately report any signs and symptoms of infection to their prescriber during Ponvory treatment and for up to 1 week after the last dose of Ponvory.
- The patient's vision should be checked prior to treatment initiation; patients should immediately report any signs and symptoms of visual impairment to their prescriber during Ponvory treatment and for up to 1 week after treatment ends.
- Ponvory must not be used during pregnancy or in women of childbearing potential who are not using effective contraception. Women of childbearing potential should:
  - Be informed by their prescriber about the risk of harmful effects to the fetus associated with Ponvory treatment both before treatment initiation and regularly thereafter.
  - Have a negative pregnancy test before starting treatment with Ponvory.
  - Use effective contraception during Ponvory treatment and for at least 1 week after treatment with Ponvory ends. Patients are advised to talk to their doctor about reliable methods of contraception.
  - Be informed by their prescriber that disease activity may return when treatment with Ponvory is stopped due to pregnancy or attempting to conceive.
  - Report immediately to their prescriber any pregnancy (intended or unintended) that occurs during Ponvory treatment or for up to 1 week after treatment with Ponvory ends.
  - Immediately stop Ponvory treatment if they become pregnant during treatment.
  - Not use Ponvory during breast-feeding.

    Refer to the pregnancy-specific patient reminder card for further information and guidance related to contraception, pregnancy, and breast-feeding.
- Liver function tests should be performed prior to treatment initiation; patients should immediately report any signs or symptoms suggestive of hepatic dysfunction (eg, nausea, vomiting, stomach pain, tiredness, loss of appetite, yellowing of the skin or the whites of the eyes, dark urine) to their prescriber.
- Patients should immediately report any signs or symptoms of new or worsening breathing problems (eg, shortness of breath) to their prescriber.
- Blood pressure should be regularly monitored during treatment with Ponvory.
- Skin cancers have been reported in patients treated with Ponvory. Patients should limit their exposure to sunlight and UV light, for example, by wearing protective clothing and applying sunscreen with a high sun protection factor regularly. Patients should inform their prescriber immediately if any skin nodules (eg, shiny, pearly nodules), patches, or open sores that do not heal within weeks develop. Symptoms of skin cancer may include abnormal growth or changes of skin tissue (eg, unusual moles) with a change in color, shape, or size over time.

- Patients should inform their prescriber about a pre-existing history or family history of epilepsy.
- Patients should immediately report any signs or symptoms suggestive of PRES (ie, sudden severe headache, sudden confusion, sudden loss of vision or other changes in vision, seizure) to their prescriber.

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

- Ponvory is contraindicated during pregnancy and in women of childbearing potential not using effective contraception.
- Prescribers will provide counseling before treatment initiation and regularly thereafter regarding the harmful effects to the fetus of Ponvory and required actions to minimize this risk.
- Women of childbearing potential must use effective contraception during Ponvory treatment and for at least 1 week after treatment ends. Patients are advised to talk to their doctor about reliable methods of contraception.
- A pregnancy test must be carried out and negative results verified by the prescriber before starting treatment with Ponvory. Pregnancy testing must be repeated at suitable intervals during treatment.
- If a woman becomes pregnant, suspects she is pregnant, or decides to become pregnant, treatment with Ponvory must be stopped immediately and medical advice regarding the risk of harmful effects to the fetus should be sought. Follow-up examinations should be performed. Patients should report immediately to their prescriber any pregnancy (intended or unintended) that occurs during Ponvory treatment or for up to 1 week after treatment with Ponvory ends.
- Ponvory must be stopped at least 1 week before attempting to conceive.
- Disease activity may return when treatment with Ponvory is stopped due to pregnancy or attempting to conceive.
- Women exposed to Ponvory during pregnancy are encouraged to join the Ponesimod Pregnancy Outcomes Program Utilizing Enhanced Pharmacovigilence Monitoring (POEM) that monitors outcomes of pregnancy.
- Ponvory should not be used during breast-feeding.